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Terpenes: Sesqui.



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1. terpenes (2) sesquiterpenes
3. hydrocarbons (4) alcohols
5. aldehydes (6) ketones
7. lactones (8) oxide
9. phenols (10) acids
11. keto oxide

Thurs.



THE TERPENES

VOLUME III



THE TERPENES

VOLUME III

The Sesquiterpenes, Diterpenes and their Derivatives

BY

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With Addenda to Volumes I and II

BY

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AND

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CAMBRIDGE

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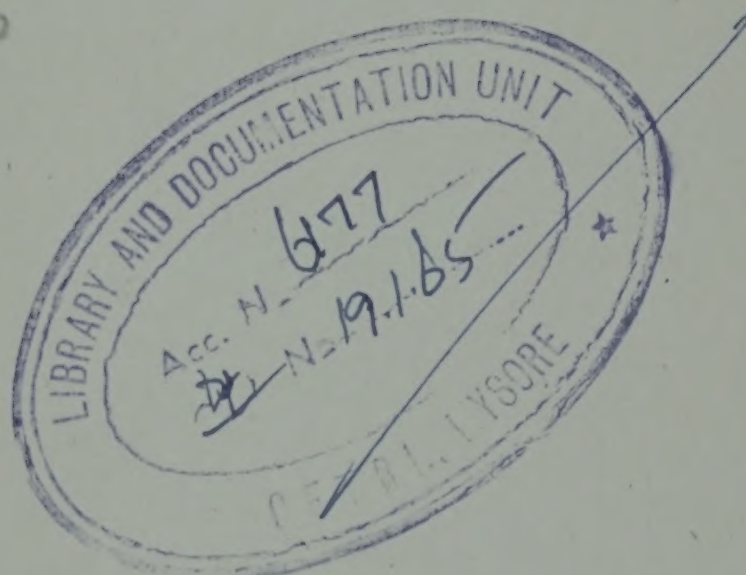
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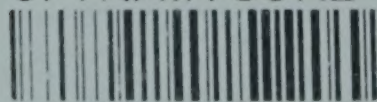
Bentley House, 200 Euston Road, London, N.W. 1
American Branch: 32 East 57th Street, New York 22, N.Y.
West African Office: P.O. Box 33, Ibadan, Nigeria

First Edition (as Volume II) 1932
Second Edition (as Volume III) 1951
Reprinted 1961

E1, 68
N53.3



CFTRI-MYSORE



6177

Terpenes: Sesqui..

First printed in Great Britain at the University Press, Cambridge
Reprinted by offset-lithography by Billing & Sons Ltd, Guildford

PREFACE

As was mentioned in the Preface to Volume II, the great increase in our knowledge of the chemistry of the sesquiterpenes, due largely to the brilliant investigations of Professor L. Ruzicka and his collaborators, has made necessary the issue of a third volume. We have taken the opportunity to add sections on the sesquiterpenoid lactones and the diterpenes. Advantage has been taken of the publication of this volume to include addenda bringing Volumes I and II up to date.

Although the manuscript was completed in 1947, through the co-operation of the Press we have been able to consult all the literature published during 1948 and 1949 and to make some reference to papers appearing in 1950.

We are indebted to Professor W. Cocker for his help in the preparation of the article on santonin, and we wish also to thank Mrs J. K. Barton for secretarial assistance and Mr C. J. W. Brooks for preparing the author and subject indexes and for checking the literature references.

J. L. SIMONSEN
D. H. R. BARTON
L. N. OWEN

LONDON

November 1950

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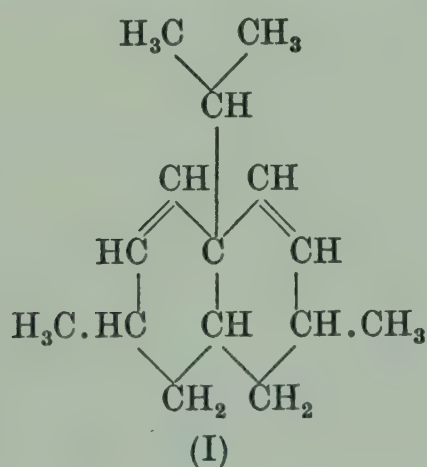
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PART I

THE SESQUITERPENES AND THEIR DERIVATIVES

INTRODUCTION

The name sesquiterpene is applied to the hydrocarbon constituents of the essential oils which have the composition $C_{15}H_{24}$. There are in the literature over four hundred references to the occurrence in nature of sesquiterpenes, but in comparatively few instances have these been characterised and shown to be homogeneous substances. Although the presence of sesquiterpenes and sesquiterpene camphors (alcohols, $C_{15}H_{24}O$ and $C_{15}H_{26}O$) was early recognised,* it is only within the last 30 years that the chemistry of these substances has been placed on a satisfactory basis. Following the valuable pioneering researches of Gladstone,[†] Wallach[‡] was the first to suggest a general formula for the sesquiterpenes. As a guiding principle he adopted the view that the sesquiterpenes, like the simpler terpenes, were built up of isoprene nuclei[§] and by the combination of three such nuclei he devised the structure (I), which represented them as derivatives



* *Inter al.* Dumas, *Annalen*, 1833, 6, 245; 1834, 9, 56; Souberain and Capitaine, *ibid.* 1840, 34, 311.

[†] *J.C.S.* 1864, 17, 1; 1872, 25, 1; 1886, 49, 609.

[‡] *Annalen*, 1887, 238, 78; 239, 49.

[§] Wallach did not assume that isoprene, as such, was involved in the formation of the hydrocarbons in nature; it was used to illustrate the arrangement of the carbon atoms in the pentane nucleus. It is in this sense that the term "isoprene nuclei" is used here.

of a partially hydrogenated substituted naphthalene. This interpretation was not intended to apply to any particular hydrocarbon, but only to show their general type. Although this arrangement of the isoprene nuclei has since been shown to be incorrect, almost all the sesquiterpenes, whose constitutions have been determined, have been shown to contain three such nuclei and Wallach's suggestion was of fundamental importance.

It is only recently that an exception, eremophilone (see p. 212), to this generalisation has been discovered.

Semmler* and Schreiner and Kremers† advanced independently a classification of the sesquiterpenes, which has proved of great value in this field of research. From a consideration of the molecular refraction of the hydrocarbons, it was possible to divide them into four main classes, which are shown in the table:

	d^{15°	$n_D^{15^\circ}$	$[R_L]_D$
(i) Acyclic (four ethylenic linkages)	0.84	1.53	69.5
(ii) Monocyclic (three ethylenic linkages)	0.89–0.87	1.51–1.49	67.8
(iii) Dicyclic (two ethylenic linkages)	0.92–0.90	1.51–1.50	66.1
(iv) Tricyclic (one ethylenic linkage)	0.935–0.91	1.49–1.50	64.4

It will be observed that, although the refractive index shows comparatively little variation, this does not apply to the density, which, however, is relatively constant within each group.

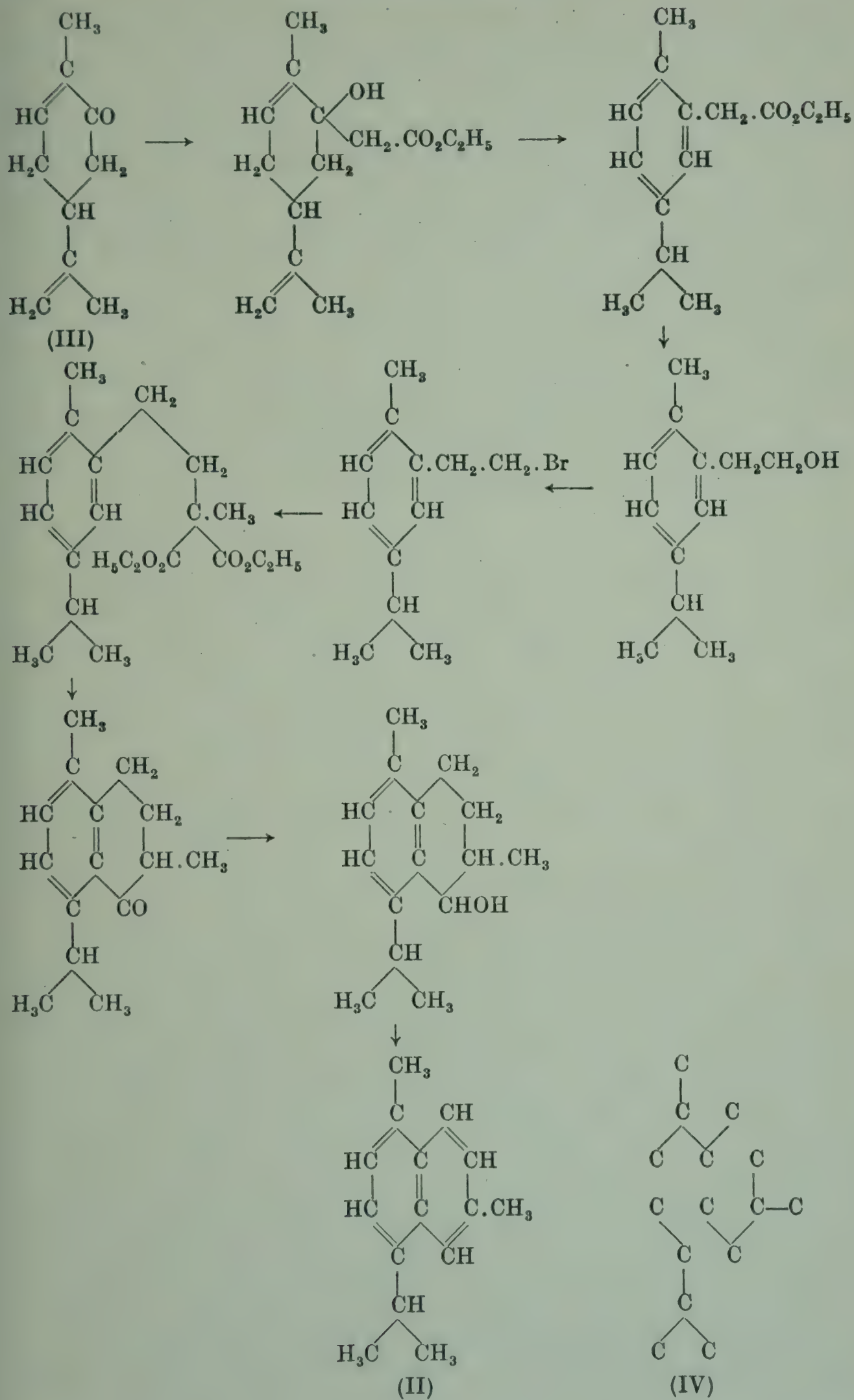
Semmler and his collaborators undertook a prolonged series of investigations into the constitutions of the various sesquiterpenes and sesquiterpene alcohols. They suggested in many cases formulae for these but, except in the case of α -santalene and α -santalol, they were purely hypothetical and devoid of experimental foundation, and up to the year 1920 the constitution of only one sesquiterpene alcohol, farnesol (p. 115), had been determined. The ordinary methods of oxidation had been unsuccessful, either because the products obtained were too simple to throw any light on the constitution of the parent body, or because they were too complex to admit of separation and identification.

The experimental researches of Ruzicka and his collaborators‡ completely revolutionised the position and they have provided a firm basis for the subsequent work in this field. Although Wallach's suggestion, that the sesquiterpenes were derivatives

* *Ber.* 1903, 36, 1037.

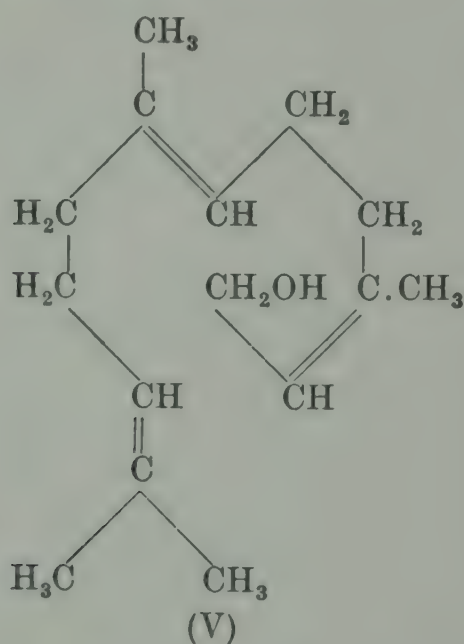
† *The Sesquiterpenes*, Milwaukee, 1904.

‡ Ruzicka, *Über Konstitution und Zusammenhänge in der Sesquiterpenreihe*, 1928.



of naphthalene, had been adopted by Semmler, all attempts to obtain substituted naphthalenes from these hydrocarbons had been unsuccessful. Ruzicka and Meyer* made the fundamental observation that cadinene gave on dehydrogenation with sulphur† the naphthalene hydrocarbon *cadalene*, 1:6-dimethyl-4-isopropyl*naphthalene* (II), the constitution of which was established by its synthesis from carvone (III) by the reactions outlined in the scheme set out on p. 3.‡

This naphthalene hydrocarbon contains all the carbon atoms present in cadinene and it will be seen that it can be dissected, in agreement with Wallach's original suggestion, into three isoprene nuclei (IV). This naphthalene hydrocarbon was potentially present in the only sesquiterpene alcohol, farnesol (V); whose constitution was known at the time.



Ruzicka, Meyer and Mingazzini§ observed, however, that when eudesmol (p. 145) and selinene (p. 32) were dehydrogenated, they did not give cadalene but another naphthalene hydrocarbon, *eudalene*, 1-methyl-7-isopropyl*naphthalene* (VII), containing a —CH₃ group less than cadalene. This hydrocarbon was synthesised by Ruzicka and Stoll|| from ethyl

* *Helv. Chim. Acta*, 1921, 4, 505.

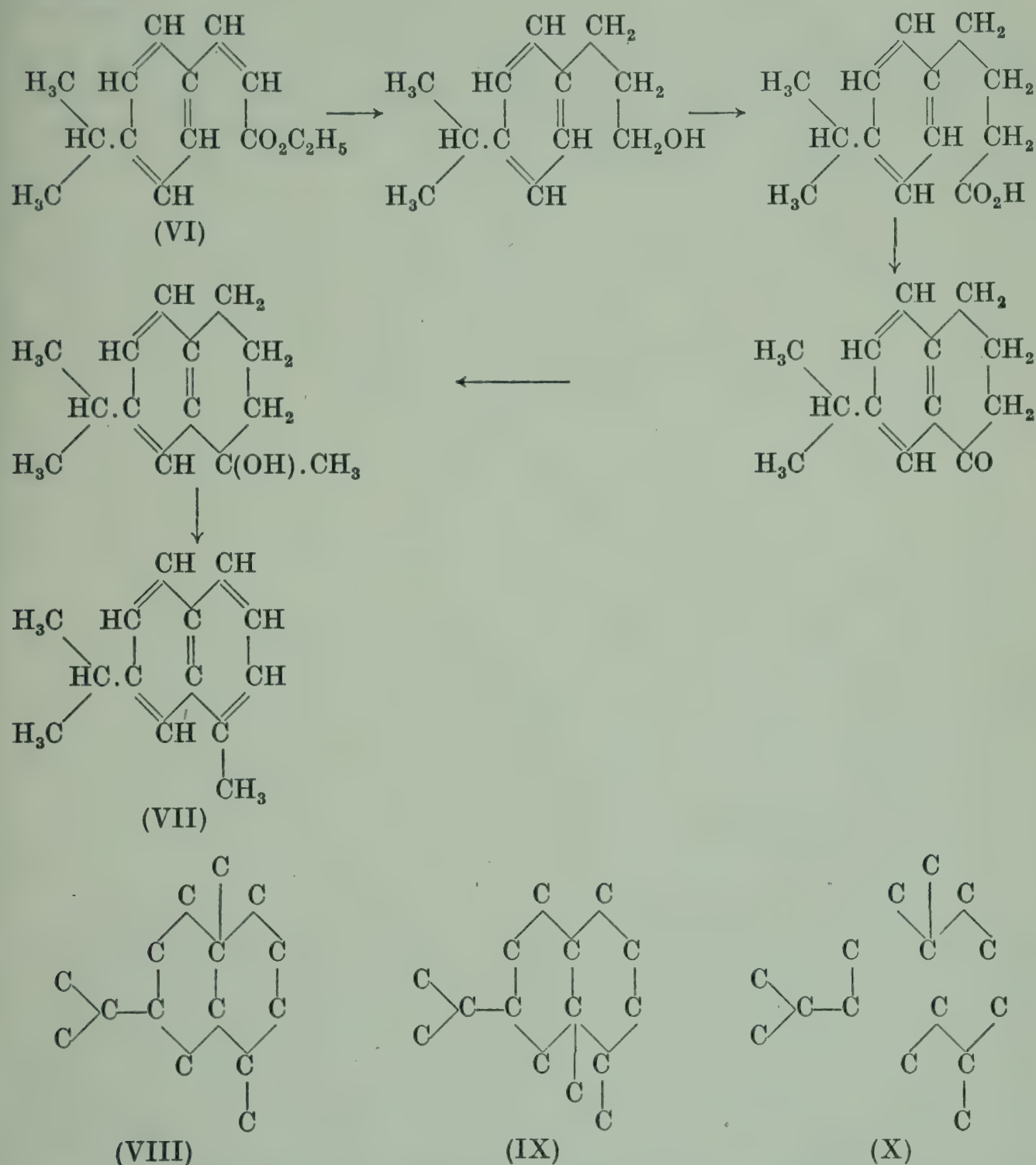
† The first use of sulphur for the dehydrogenation of terpene derivatives was due to Vesterberg (*Ber.* 1903, 36, 4200), who investigated its action on abietic acid (compare Ruzicka, *op. cit.* p. 9).

‡ Ruzicka and Seidel, *Helv. Chim. Acta*, 1922, 5, 369.

§ *Helv. Chim. Acta*, 1922, 5, 345.

|| *Ibid.* 1922, 5, 923; for more recent syntheses see Chakravarti, *J. Ind. C.S.* 1943, 20, 393; Darzens and Levy, *Compt. rend.* 1932, 194, 2056; Barnett and Sanders, *J.C.S.* 1933, 434.

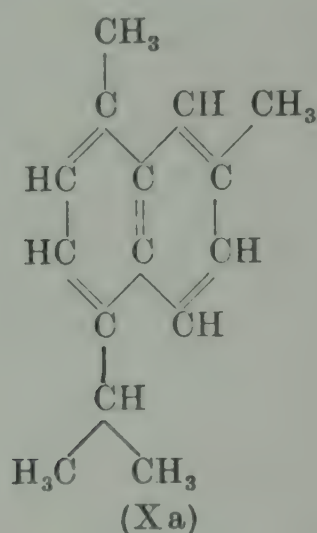
p-isopropylcinnamate (VI) by the reactions shown in the scheme:



It is obvious that the carbon atom eliminated from the sesquiterpene during the process of dehydrogenation must have been present as a methyl group in either position 9 or 10 in the naphthalene nucleus, so that the skeleton of the parent hydrocarbon may be represented by either (VIII) or (IX). Of these two possibilities only (VIII) need be considered, since it can be built up from three isoprene nuclei as indicated by (X); which is not possible if the structure (IX) is adopted.*

* Eremophilone is an exception to this reasoning, see p. 212.

In an important investigation Šorm and Urbánek* have very recently shown that the structure of the sesquiterpene alcohol, carotol, is based on a hitherto unknown type of carbon skeleton, represented by its dehydrogenation product 1:7-dimethyl-4-isopropylnaphthalene (Xa). The synthesis of the latter has already been recorded by Rapson and Short.†



Ruzicka, Schinz and Müller‡ have recently described the isolation of a novel substituted naphthalene by dehydrogenation of the sesquiterpene from the essential oil of the leaves of *Cedrus atlantica* Manetti. This hydrocarbon is either a *pentamethyl-* or a *trimethylethyl*naphthalene, and is formed in small amount as compared with the major product of the dehydrogenation which is 1:6-dimethylnaphthalene.

A careful study of physical properties has enabled Ruzicka, Koolhaas and Wind§ to conclude that cadinene (p. 25), selinene (p. 32), and therefore eudesmol (p. 145) and cadinol (p. 136) are derivatives of *cis*-decalin rather than of the energetically more stable *trans*-decalin.|| The stereochemistry of the various sesquiterpenoid lactones and their derivatives is relatively well understood and is discussed in detail under the respective compounds.

Although many sesquiterpenes have now been shown to contain a potential naphthalene skeleton, an important class of sesquiterpenes built up on an azulenic framework has come to be recognised in more recent years. It had, of course, long been known that the higher boiling fractions of many essential oils contained blue azulenic hydrocarbons, but it had not been

* *Coll. Czech. Chem. Comm.* 1948, **13**, 49.

† *J.C.S.* 1933, p. 728.

‡ *Helv. Chim. Acta*, 1944, **27**, 195.

§ *Ibid.* 1931, **14**, 1171.

|| Compare the caryophyllenes, p. 39.

possible to relate them to the other members of the oils until the basic structure of the azulenes had been characterised.* It was, therefore, of peculiar interest when it was found that this carbon skeleton formed the basis of a number of sesquiterpenes. The best characterised members of this group are guaiol (p. 156) and β -vetivone (p. 224). On dehydrogenation with sulphur a number of sesquiterpenoid substances including guaiol furnish S-guaiazulene[†] (XI), 1:4-dimethyl-7-isopropylazulene, the synthesis of which has been recently reported by Plattner, Fürst and Marti.[‡] The α - and β -vetivones and various derivatives thereof give, on treatment with dehydrogenating agents, *vetivazulene*, which has been shown to be 2-isopropyl-4:8-dimethylazulene (XII). This hydrocarbon has been synthesised by Pfau and Plattner[§] and by Coats and Cook.^{||} The method used by the former workers is indicated in the scheme on p. 8. The formulae of S-guaiazulene and *vetivazulene* correspond to two of the various ways of arranging three isoprene units into an azulenic skeleton.

Although the method of determining ring structure in sesquiterpenes by dehydrogenation has been of the greatest value, it is by no means of general application. It fails completely for example with the tricyclic cedrene (p. 75) and the bicyclic β -caryophyllene (p. 40) and in such cases the laborious methods of stepwise oxidative degradation have to be employed. A most useful extension of the dehydrogenation procedure, which enables the position of double bonds in sesquiterpenes of known skeletal structure to be determined without ambiguity, has recently been made by Soffer and his collaborators[¶] (see pp. 12, 27), and further applications of this method are to be anticipated. In spite of the limitations of all dehydrogenation experiments, it can be safely said that much of the work described in the sequel could not have been brought to a successful conclusion without their help.

* See *inter al.* Wagner-Jauregg, Friess, Hippchen and Prier, *Ber.* 1943, **76**, 1157; Arnold, *Die Chemie*, 1943, **56**, 7; Haworth, *Ann. Rep. C.S.* 1937, **34**, 393; Pfau and Plattner, *Helv. Chim. Acta*, 1936, **19**, 858; Ruzicka and Haagen-Smit, *ibid.* 1931, **14**, 1104; Ruhemann and Lewy, *Ber.* 1927, **60**, 2459; Ruzicka and Rudolph, *Helv. Chim. Acta*, 1926, **9**, 118.

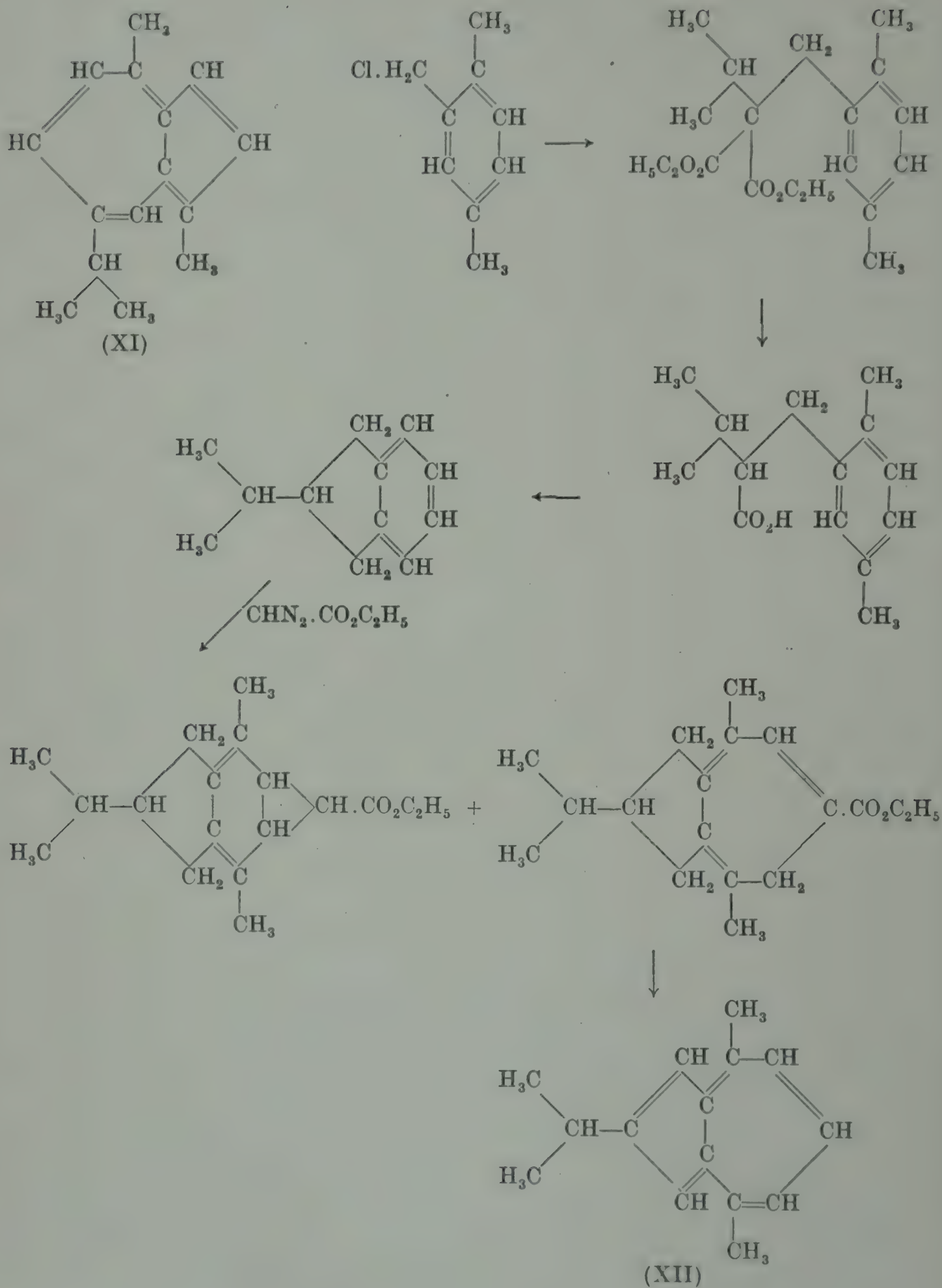
[†] See especially Pfau and Plattner, *Helv. Chim. Acta*, 1936, **19**, 858.

[‡] *Helv. Chim. Acta*, 1949, **32**, 2452.

[§] *Ibid.* 1939, **22**, 202.

^{||} *J.C.S.* 1942, p. 559.

[¶] *J. Amer. C.S.* 1942, **64**, 417; 1944, **66**, 1520.

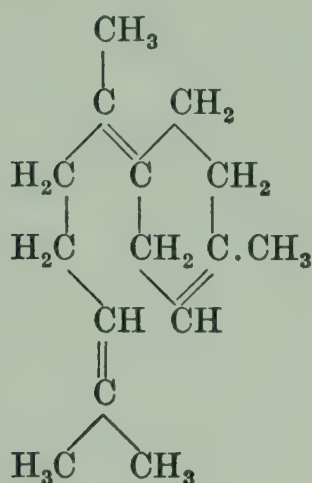


CHAPTER I

HYDROCARBONS

A. MONOCYCLIC HYDROCARBONS

BISABOLENE



Bisabolene, $C_{15}H_{24}$, is the sesquiterpene which, with the exception of cadinene and caryophyllene, occurs most widely distributed in nature. It was first isolated by Tucholka* from bisabol myrrh and later by Burgess and Page† from oil of bergamot.‡ Its presence in a large number of other essential oils has since been established.§ Bisabolene can be characterised by the preparation of a *trihydrochloride*, m.p. $79-80^{\circ}$, from which it can be regenerated by the action of sodium acetate in acetic acid solution.

Although the preparation of this trihydrochloride showed that bisabolene was a monocyclic hydrocarbon containing three ethylenic linkages, the first evidence of its structure was obtained from the investigations of Ruzicka and Capato,|| who showed that it must be represented by formula (I), (II) or (III), since it could be prepared by the dehydration of *dl*-nerolidol (p. 121). The identity of the natural and synthetic hydrocarbons was confirmed by a comparison of their trihydrochlorides.

* *Arch. Pharm.* 1897, 235, 289.

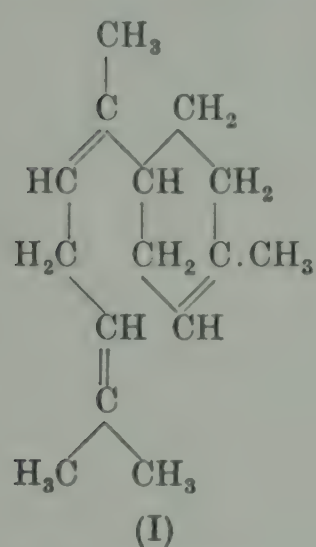
† *J.C.S.* 1904, 85, 1327.

‡ The name, limene, used by these authors must be replaced by bisabolene, since Tucholka's hydrocarbon is identical with that of Burgess and Page.

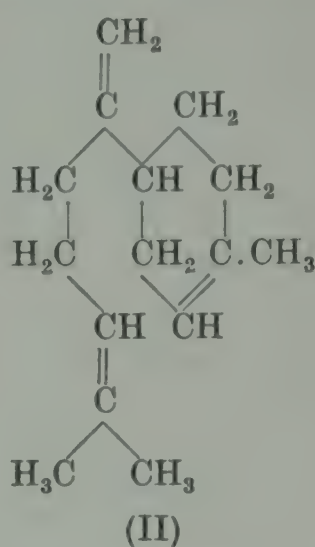
§ Ruzicka and Capato, *Helv. Chim. Acta*, 1925, 8, 263.

|| *Ibid.* p. 259.

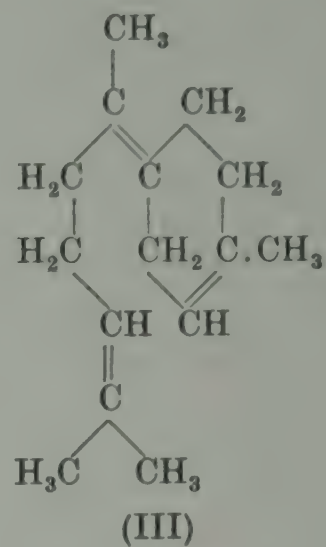
Ruzicka and van Veen* found later that both the natural and synthetic hydrocarbons consisted essentially of γ -bisabolene (III). When bisabolene, which had been regenerated from the trihydrochloride, was oxidised with ozone in acetic acid solution



(α -Bisabolene)

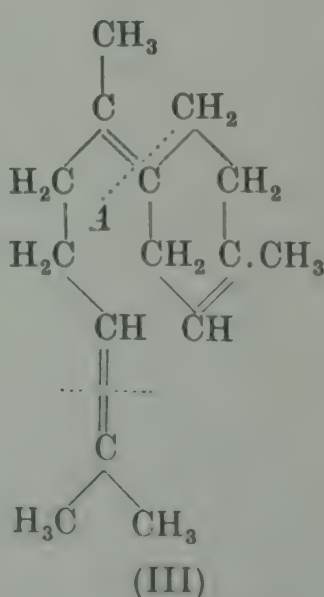
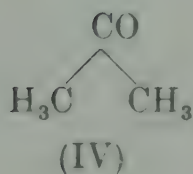
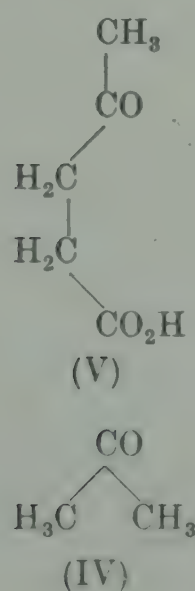


(β -Bisabolene)



(γ -Bisabolene)

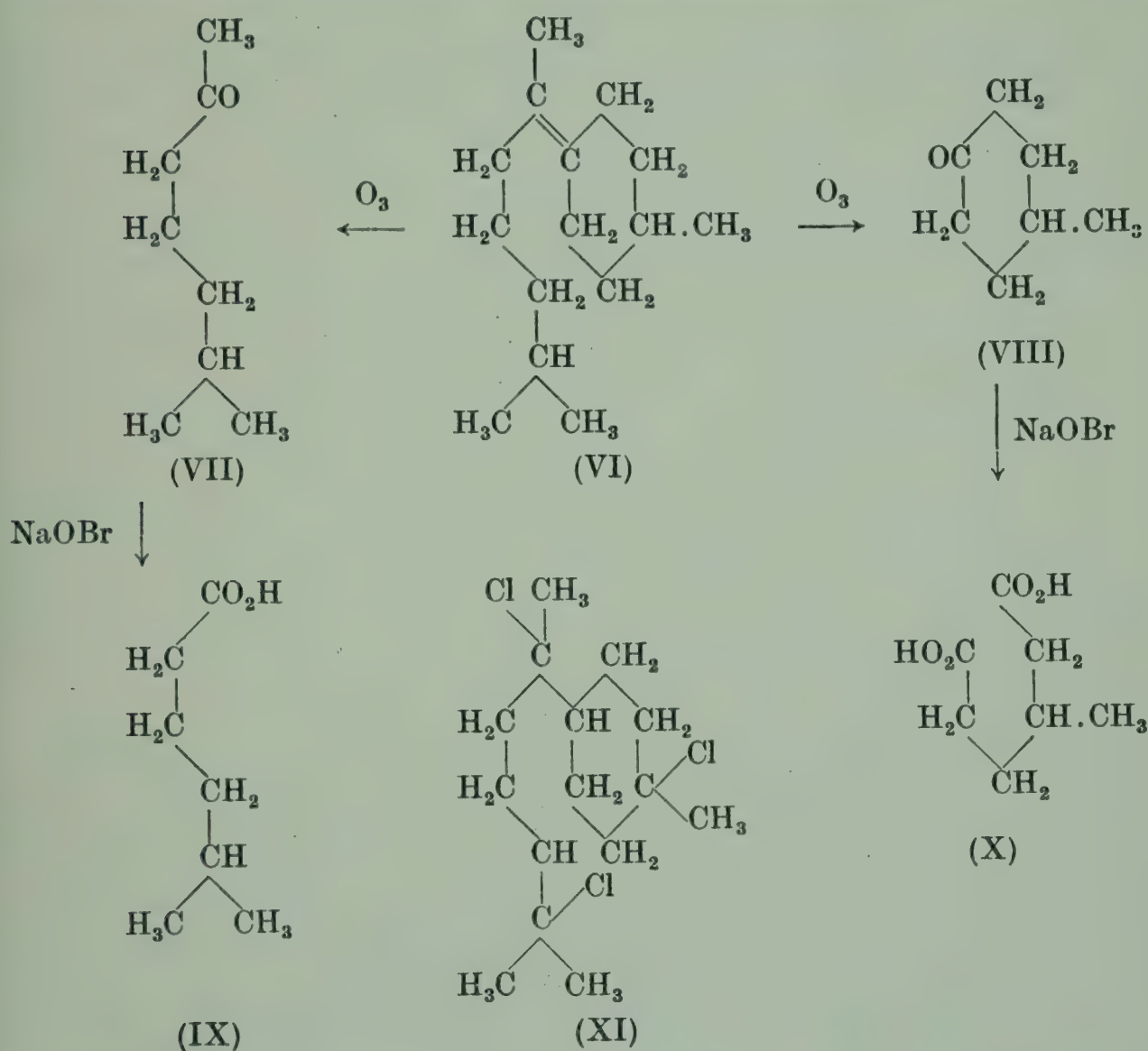
a mixture of acetone (IV) and levulinic acid (V), together with some succinic acid, was obtained. These substances would result directly from the ozonolysis of (III), but it is not possible to explain the formation of levulinic acid without a very complete degradation of either (I) or (II). The complete absence of formaldehyde and of formic acid proved that a hydrocarbon having the structure (II) was not present.



Direct evidence of the occurrence of the ethylenic linkage, A in (III), was obtained in the following manner. It had been

* *Annalen*, 1929, 468, 133, 143.

observed by Semmler and Rosenberg* that bisabolene, on hydrogenation in acetic acid solution in the presence of platinum black, gave *hexahydrobisabolene*, b.p. 123–125°/8 mm., d^{20}_D 0.8244, n_D 1.45423. If, however, *cyclohexane* was used as the solvent, then *tetrahydrobisabolene* (VI), b.p. 125°/15 mm., d^{15}_4 0.857, was obtained. On ozonolysis this hydrocarbon yielded a mixture of *methylheptanone* (VII) and 4-methylcyclohexanone (VIII), which were identified by their oxidation with sodium hypobromite to *isoamylacetic acid* (IX) and β -methyladipic acid (X) respectively.



Since the experiments outlined above were carried out both with natural bisabolene and with bisabolene regenerated from the trihydrochloride, there can be no doubt that the sesquiterpene has the structure represented by (III). It is of course possible, as Ruzicka and van Veen have pointed out, that this does not apply to all natural bisabolenes.

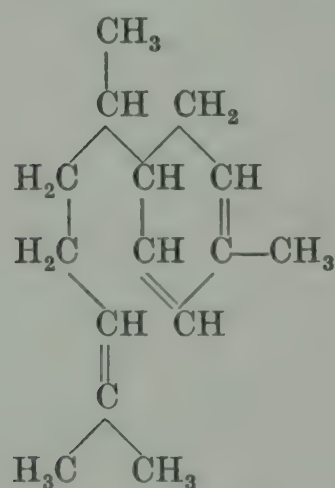
* *Ber.* 1913, 46, 769.

Bisabolene trihydrochloride (XI) has been prepared by an unambiguous synthesis by Ruzicka and Liguori.*

Bisabolene is a colourless viscid oil, which, when regenerated from the trihydrochloride, has the constants, b.p. 133–134°/12 mm., $d_4^{21^\circ}$ 0.8717, $n_D^{21^\circ}$ 1.4923. As is to be anticipated from its constitution, the molecular refraction, 67.99, shows little exaltation over the calculated value 67.87.

In addition to the trihydrochloride, bisabolene yields a *tri-hydrobromide*, m.p. 84°,† whilst Schmidt and Weilinger‡ have described a *hexabromide*, m.p. 154°. It does not give a naphthalene derivative on dehydrogenation with sulphur or selenium, nor does it react with ethyl diazoacetate.

ZINGIBERENE



The main constituent of ginger oil (from the rhizomes of *Zingiber officinale* Roscoe) is the monocyclic sesquiterpene, zingiberene, $C_{15}H_{24}$. Possibly owing to the difficulties associated with its identification, it has only been found to be present in two other botanically related oils, those obtained from the rhizomes of *Curcuma Zedoaria*§ and *Curcuma longa*.|| Zingiberene was first described by Thresh¶ and was more thoroughly investigated by v. Soden and Rojahn** and by Schreiner and Kremers.††

The first attempts to determine its constitution were due to Semmler and Becker.‡‡ From its physical constants, b.p.

* *Helv. Chim. Acta*, 1932, 15, 3.

† Wallach, *Annalen*, 1909, 368, 20.

‡ *Ber.* 1906, 39, 657.

§ Rao, Shintre and Simonsen, *J.S.C.I.* 1928, 47, 171 T.

|| Kelkar and Rao, *J. Ind. Inst. Sci.* 1933, 17 A, 7.

¶ *Pharm. J.* 1881, 12, 721.

** *Pharm. Ztg*, 1900, 45, 414.

†† *Pharm. Arch.* 1901, 4, 63, 141, 161.

‡‡ *Ber.* 1913, 46, 1816.

134°/14 mm., d^{20}_D 0.8684, n^{20}_D 1.4956, $[\alpha]_D$ -73.38°, $[R_L]_D$ 68.37, $C_{15}H_{24}$, $\epsilon_3 = 67.86$, it was evidently a monocyclic terpene containing three ethylenic linkages. The large molecular exaltation indicated that two of these were probably conjugated, and support was lent to this by the preparation of a *dihydrochloride*, m.p. 168°, and a liquid *tetrabromide*, whilst on reduction with sodium in alcoholic solution *dihydrozingiberene*, $C_{15}H_{26}$, b.p. 122–125°/7 mm., d^{20}_D 0.8557, n_D 1.4837, $[\alpha]_D$ -37°, was obtained. This hydrocarbon no longer shows any molecular exaltation. The presence of a conjugated system of ethylenic links in zingiberene has been confirmed by an examination of its absorption spectrum.* The saturated hydrocarbon, *hexahydrozingiberene*, $C_{15}H_{30}$, b.p. 128–130°/11 mm., d^{20}_D 0.8264, n_D 1.4560, $[\alpha]_D$ -10.12°, was prepared by the catalytic hydrogenation of zingiberene in acetic acid solution in the presence of platinum. Whilst the experiments of Semmler and Becker thus showed that zingiberene was a monocyclic hydrocarbon with three ethylenic linkages, two of which were conjugated, they threw no light on its structure.

Most of the work on the elucidation of the constitution of zingiberene was carried out by Ruzicka and van Veen.† The difficulties encountered were enhanced by the observation that zingiberene from ginger oil is never homogeneous, but always contains a small quantity of bisabolene, from which it cannot be separated. The quantity of this hydrocarbon present in the mixture cannot be large for the following reasons: (i) no difficulty is experienced in obtaining pure dihydrozingiberene, although bisabolene is not reduced under the conditions used in its preparation; (ii) very little bisabolene trihydrochloride is formed when zingiberene‡ is treated with hydrogen chloride; and (iii) when zingiberene is treated with ethyl diazoacetate the greater portion of the hydrocarbon reacts, although, as mentioned on p. 12, bisabolene will not condense with this ester.

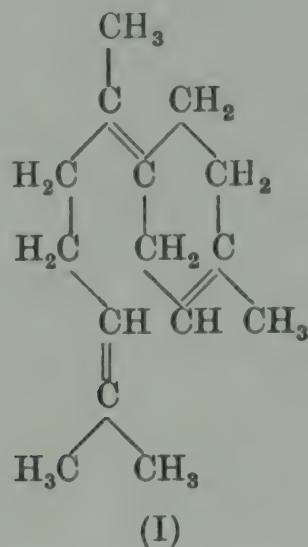
When zingiberene is oxidised with ozone it yields the same products as bisabolene (I), namely levulinic acid and acetone, together with a little succinic acid. This indicates that zingiberene probably has the same carbon skeleton as bisabolene. This was

* Booker, Evans and Gillam, *J.C.S.* 1940, p. 1453.

† *Annalen*, 1929, **468**, 143.

‡ The name zingiberene will be used for the natural hydrocarbon, although it is actually a mixture of zingiberene and bisabolene.

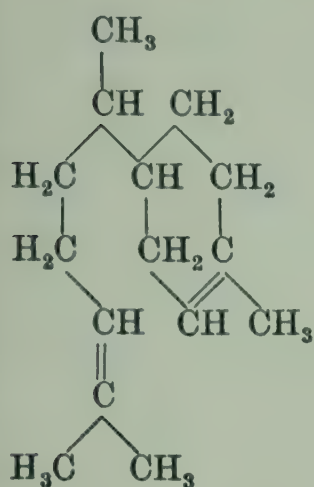
confirmed by the observation that, when zingiberene was dehydrogenated with palladium (see p. 17) and the resulting hydrocarbon oxidised with chromic acid, only terephthalic acid was obtained with no traces of either benzene tri- or tetracarboxylic acids.



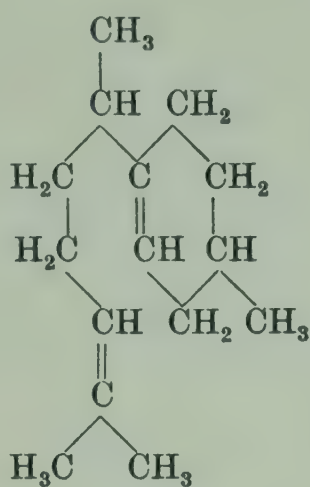
It was mentioned above that, when zingiberene was reduced with sodium in alcoholic solution, dihydrozingiberene was obtained, which results from the reduction of one of the conjugated ethylenic linkages. This hydrocarbon must be represented by either (II), (III) or (IV), since it yields on ozonolysis acetone, levulinic and succinic acids. If, however, it is oxidised with potassium permanganate in acetone solution, then an acid is obtained from which a *methyl ester*, $C_{14}H_{24}O_5$, b.p. $140-155^{\circ}/0.3$ mm., can be prepared. This must be the dimethyl ester of a *ketonic dibasic acid*, $C_{12}H_{20}O_5$, having the constitution (V), as it yields on oxidation with sodium hypobromite a *tricarboxylic acid*, $C_{11}H_{18}O_6$ (VIII). An acid of this composition can result only by the degradation of a hydrocarbon (II); a hydrocarbon (III) would yield a ketonic acid (VI), in which the carbonyl group would form part of a long chain, whilst (IV) would give rise directly to a tricarboxylic acid (VII). The relationship of zingiberene to dihydrozingiberene (II) has recently been established by Eschenmoser and Schinz.* Zingiberene has been proved to have the constitution (IX) on the basis of the following experiments. On reaction with acetylenedicarboxylic acid dimethyl ester, zingiberene afforded the *adduct* (X). This was not isolated but was subjected to pyrolysis to give 2:6-

* *Helv. Chim. Acta*, 1950, **33**, 171.

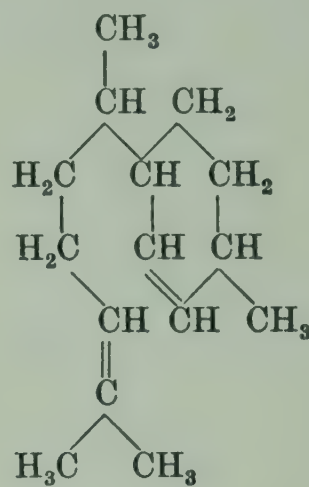
dimethylocta-2:7-diene (XI), b.p. 153–156/730 mm., n_D^{20} 1.4384, and the *dimethyl ester* (XII) of 4-*methylphthalic acid* (see p. 16).



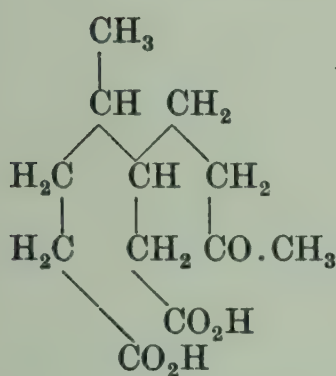
(II) \downarrow KMnO_4



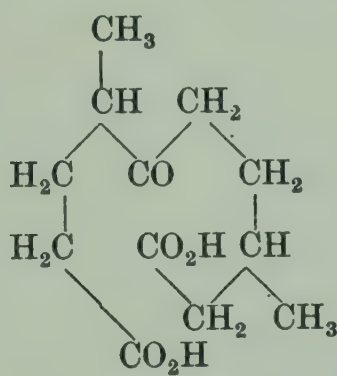
(III) $\downarrow \text{KMnO}_4$



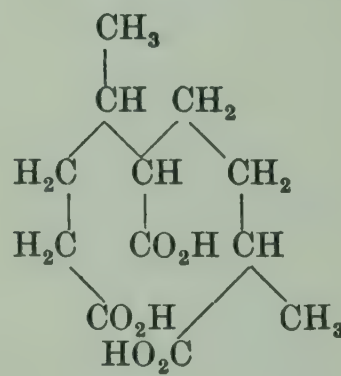
(IV) $\downarrow \text{KMnO}_4$



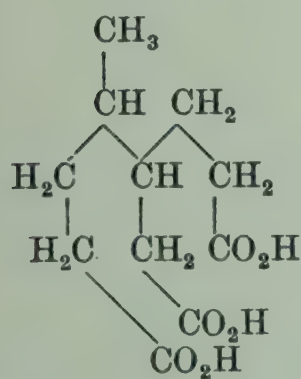
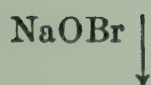
(V)



(VI)



(VII)

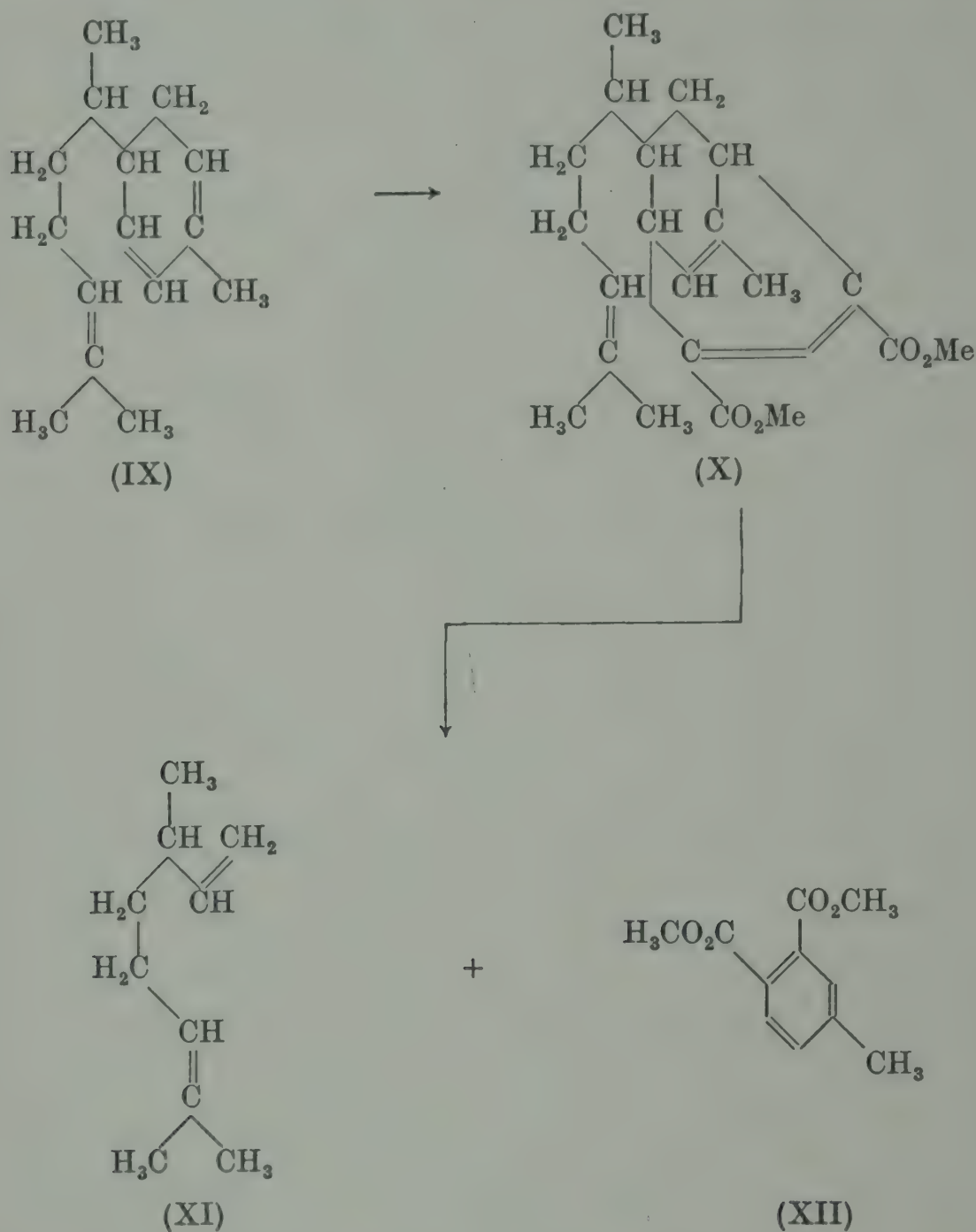


(VIII)

Zingiberene is most conveniently characterised by the preparation of the *dihydrochloride*, m.p. 169–170°. This is, however, not a true derivative of zingiberene, and, on removal of hydrogen chloride, an isomeric dicyclic hydrocarbon, *isozingiberene*, b.p. 120–123°/8 mm., d^{20}_D 0.9150, n_D 1.5034, $[\alpha]_D -41^\circ$, is obtained.*

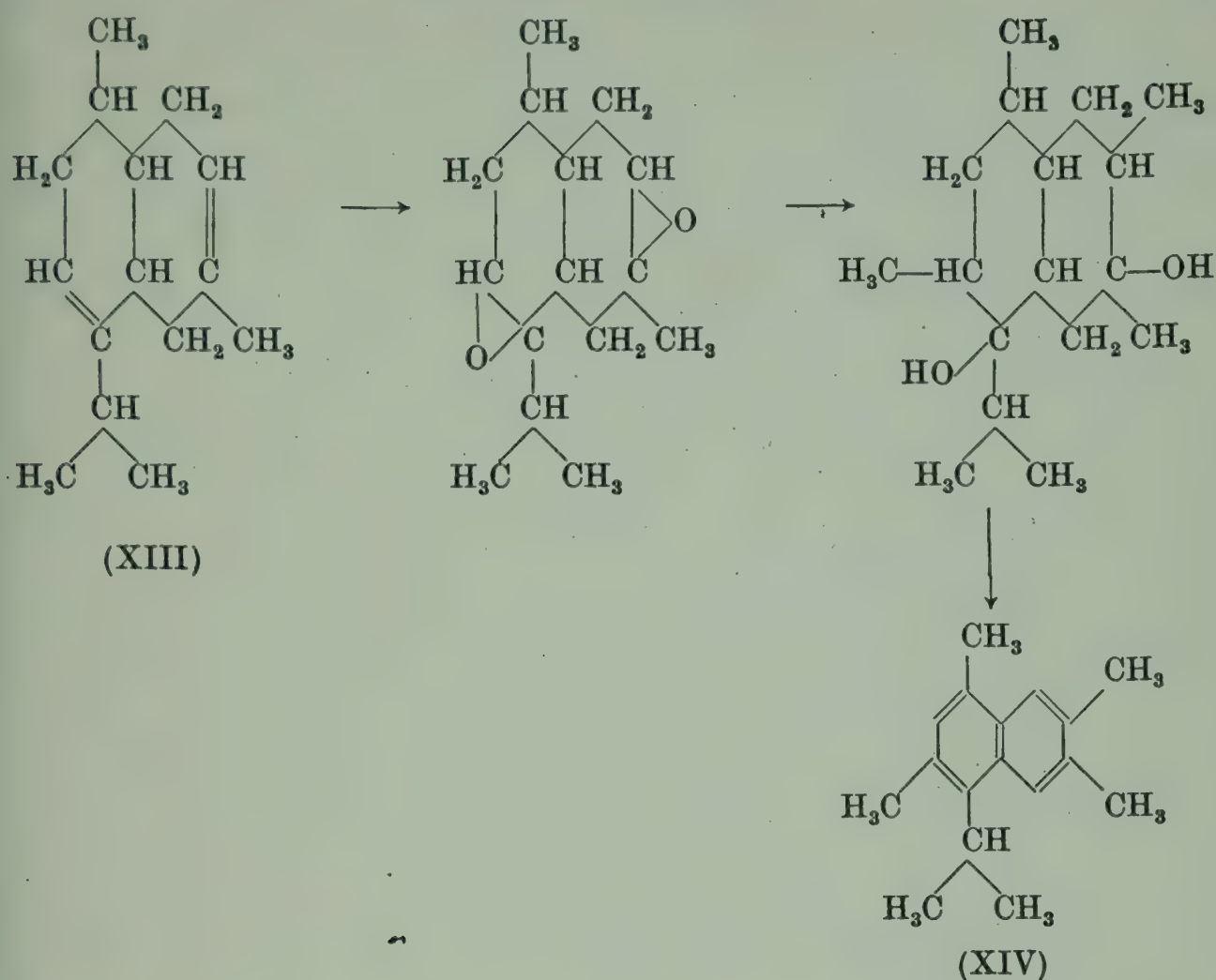
* Semmler and Becker, *Ber.* 1913, **46**, 1818.

This hydrocarbon results also when zingiberene is treated with acetic-sulphuric acid at 60°. Its constitution has been elucidated



by Soffer, Steinhardt, Turner and Stebbins,* who have conclusively proved it to be represented by (XIII). On treatment with perbenzoic acid *isozingiberene* formed a dioxide from which by the action of methyl magnesium iodide a *glycol* was obtained. Since the latter, after dehydration with formic acid and dehydrogenation with chloranil, yielded 4-*isopropyl*-1:3:6:7-tetramethylnaphthalene (XIV), m.p. 96–97°, *picrate*, m.p. 156–156.5°, the reactions must proceed according to the following scheme:

* *J. Amer. C.S.* 1944, 66, 1520.



*iso*Zingiberene cannot be reduced by sodium in alcoholic solution, but by catalytic hydrogenation *tetrahydroisozingiberene*, $C_{15}H_{28}$, b.p. $123-123.5^{\circ}/10$ mm., d^{20}_{20} 0.8822, n_D 1.4791, $[\alpha]_D + 4.36^{\circ}$, has been prepared. This hydrocarbon must be identical with tetrahydrocadinene (p. 29) and their physical constants are in good agreement.

Zingiberene is a colourless oil, which on keeping tends to resinify. When it is treated with hydrogen bromide it yields a *dihydrobromide*, m.p. 175° , which, like the dihydrochloride, is a derivative of *isozingiberene*.

Schreiner and Kremers have described a *nitrosochloride*, m.p. $93-94^{\circ}$, two *nitrosites*, m.p. $120-121^{\circ}$ and 105° , and a *nitrosate*, m.p. $86-88^{\circ}$.

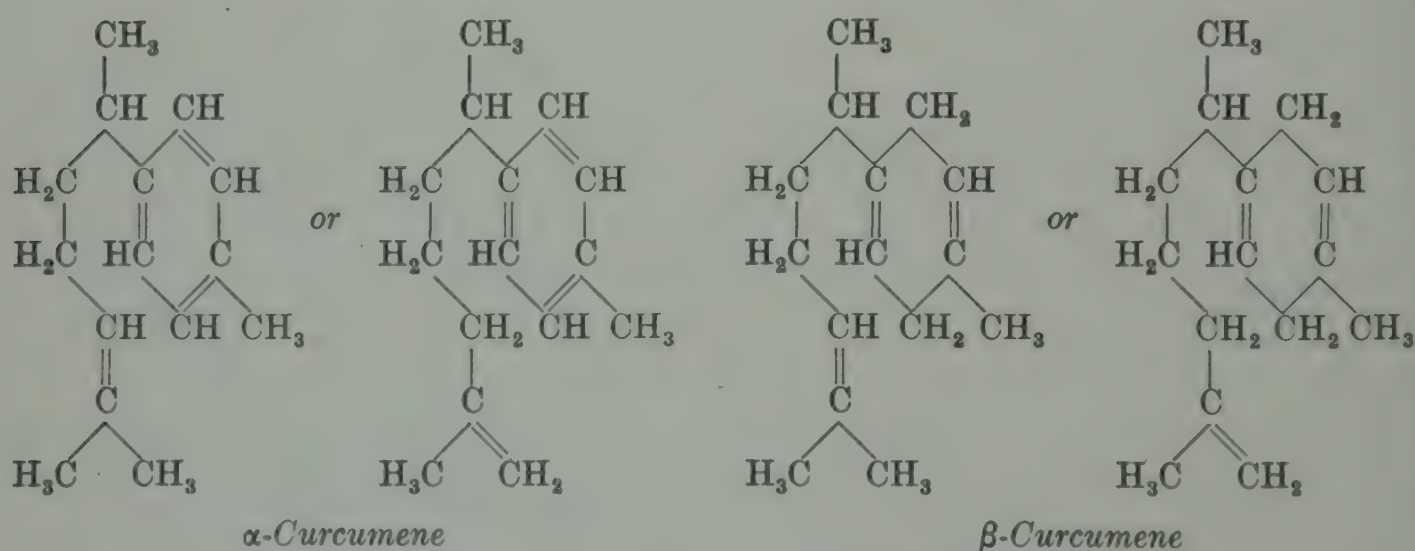
Zingiberene differs from bisabolene in that, when it is dehydrogenated with sulphur, it gives an excellent yield of cadalene.* On catalytic dehydrogenation with a palladium catalyst at $345-360^{\circ}$, 2-methyl-6-(*p*-tolyl)-heptane, b.p. $135^{\circ}/12$ mm., is obtained.

* Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 345.

Zingiberene resembles the acyclic hydrocarbon, myrcene (Vol. I, p. 16), since, when it is heated in admixture with isoprene at 215° in a sealed tube, cyclisation and polymerisation occur. Semmler and Becker* found the products of the reaction to be a dicyclic terpene, *metazingiberene*, $C_{15}H_{24}$, b.p. $100-150^{\circ}/11$ mm., $d^{20}_{20} 0.8927$, $n_D 1.4968$, $[\alpha]_D + 6.5^{\circ}$, a *diterpene*, $C_{20}H_{32}$, b.p. $150-200^{\circ}/11$ mm., $d^{20}_{20} 0.9085$, $n_D 1.5037$, $[\alpha]_D - 13^{\circ}$, formed possibly by the condensation of zingiberene and isoprene, and a *dizingiberene*, $C_{30}H_{48}$, b.p. $260-280^{\circ}/11$ mm., $d^{20}_{20} 0.9287$, $n_D 1.5187$, $[\alpha]_D - 5^{\circ}$. There is no evidence that any of the substances prepared by Semmler and Becker were homogeneous.

Brooks† has separated from ginger oil an alcohol, *zingiberol*, $C_{15}H_{26}O$, b.p. $154-157^{\circ}/14.5$ mm., which is apparently a derivative of either zingiberene or *isozingiberene*, since, on dehydration, it yields a hydrocarbon, $C_{15}H_{24}$, giving zingiberene dihydrochloride on treatment with hydrogen chloride.

THE CURCUMENES



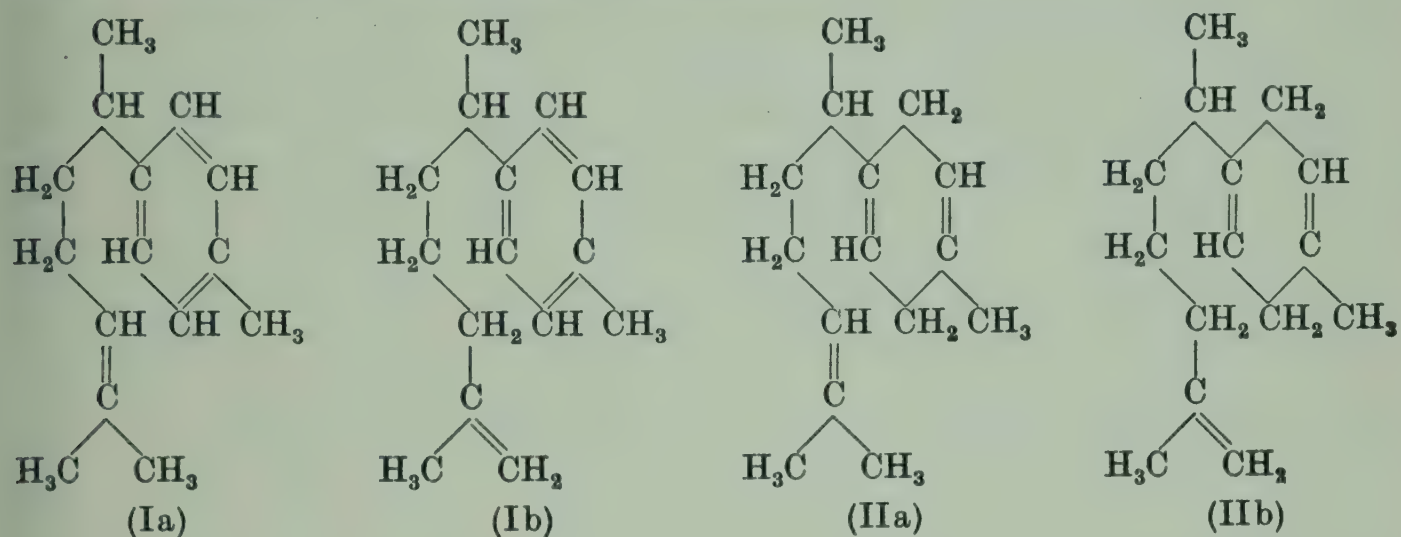
The sesquiterpene hydrocarbon constituents of the essential oil from the rhizomes of *Curcuma aromatica* Salisb. have been examined by Simonsen and his collaborators.‡ The natural product has been shown to be a complex mixture of (Ia) and (Ib), with (Ia) predominating, and of (IIa) and (IIb), with (IIa) likewise being in excess. The names formerly proposed, *1- α -curcumene* for (Ia) and (Ib) and *1- β -curcumene* for (IIa) and

* Ber. 1913, 46, 1821.

† J. Amer. C.S. 1916, 38, 430.

‡ J. Ind. Inst. Sci. 1936, 9 A, 140; J.C.S. 1928, p. 2496; *ibid.* 1939, p. 1504.

(IIb) are retained below for convenience of exposition, but they are to be understood as referring to very closely related mixtures rather than to chemical individuals. Although *l*- α -curcumene is not, strictly speaking, a sesquiterpene, an account of its chemistry is included here because of its very close relationship with *l*- β -curcumene. The constituents of these mixtures cannot be separated by fractional distillation.

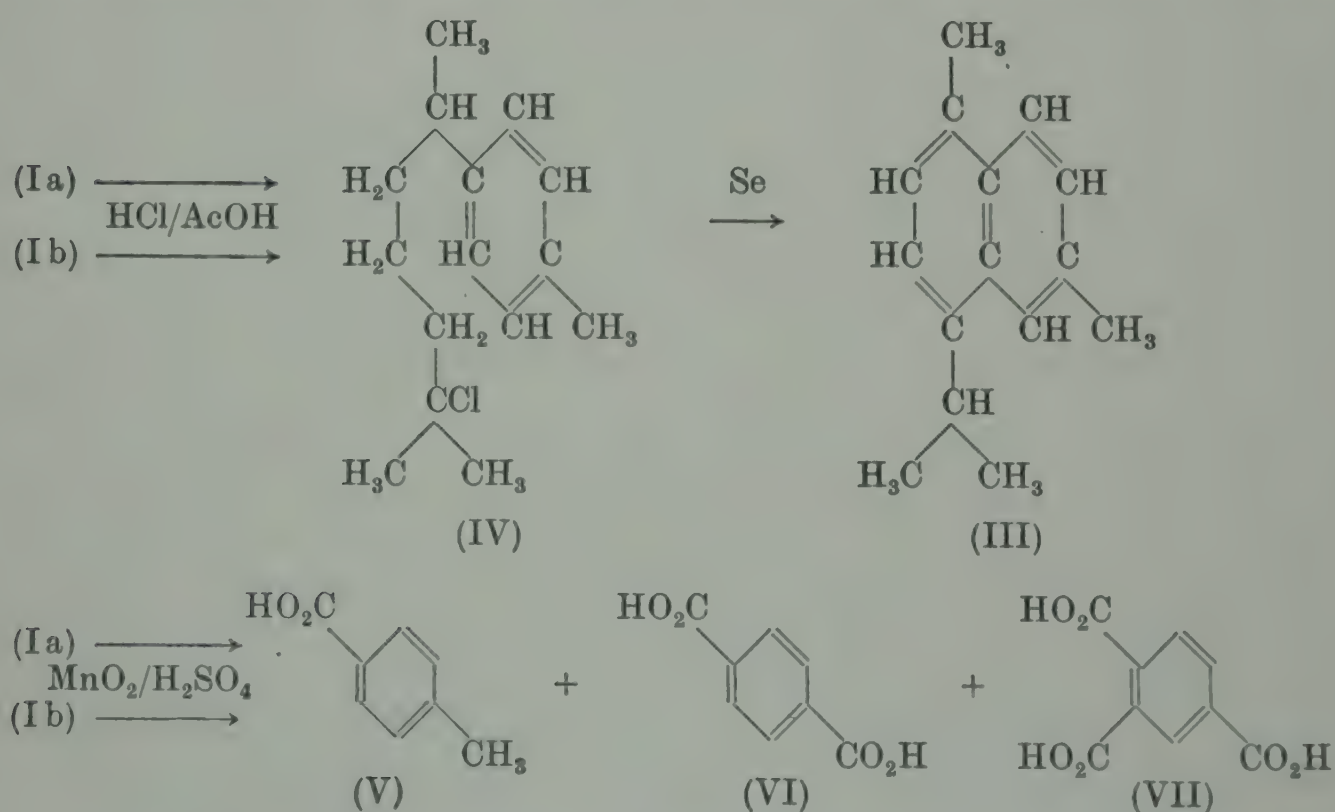


l- α -Curcumene can be separated from the original hydrocarbon mixture by two distinct methods. If the original mixture be treated with hydrogen chloride in acetic acid solution a crystalline *trihydrochloride*, derived from *l*- β -curcumene (see below) and a liquid *monohydrochloride*, b.p. 150–155°/8 mm., are obtained. The latter, when treated with sodium acetate in acetic acid solution, yields *l*- α -curcumene, b.p. 137°/17 mm., d_{20}^{20} 0.8821, n_D^{20} 1.4989, $[\alpha]_{5461} -34.3^\circ$. *l*- α -Curcumene can, however, be prepared in a higher state of purity by the following method.

The original mixture gave a *nitrosate*, m.p. 101°, $[\alpha]_{5461} -20.3^\circ$ (in chloroform) (*nitrolbenzylamine*, m.p. 102–104°, $[\alpha]_D^{30} -19.5^\circ$), which, by the action of potassium hydroxide in alcoholic solution, was converted into *l*-oximino- α -curcumene, b.p. 182–185°/7 mm., d_{30}^{30} 0.9817, n_D^{30} 1.5134, $[\alpha]_D^{30} -27.2^\circ$, *benzoyl* derivative, m.p. 84–85°. On reduction with sodium in alcoholic solution *l*-oximino- α -curcumene gave *l*-dihydro- α -curcumylamine, b.p. 153–154°/14 mm., d_{30}^{30} 0.9026, n_D^{30} 1.4983, $[\alpha]_D^{30} -22.2^\circ$, which was characterised by the preparation of a *hydrogen oxalate*, m.p. 143–144°, and an *acetyl* derivative, m.p. 109–110°. The base was converted into the *trimethylammonium iodide*, m.p. 163–164°, and the hydroxide of this, on distillation under diminished

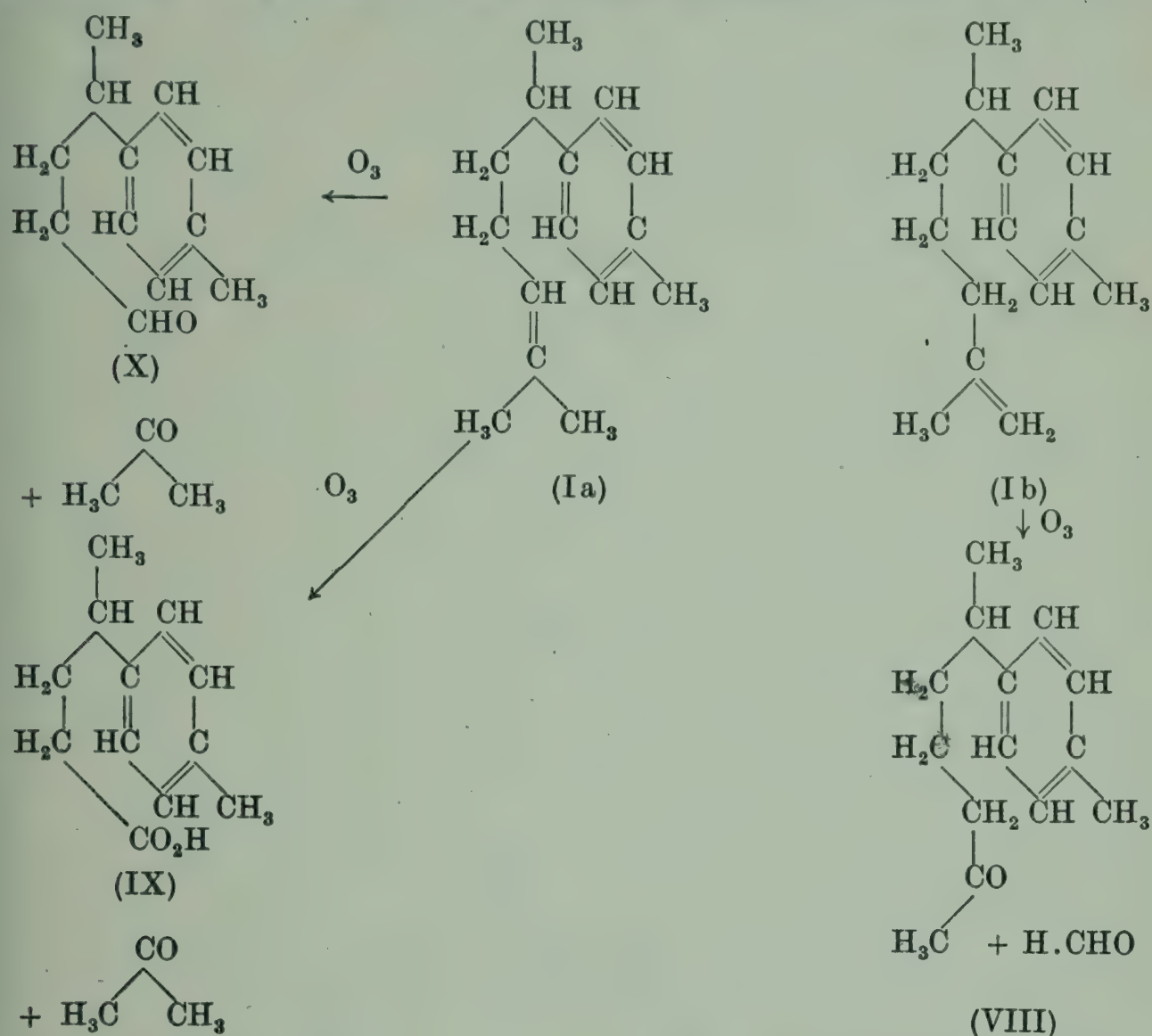
pressure, gave a mixture of *l*- α -curcumene and *l*-dimethyldihydro- α -curcumylamine, b.p. 130–140°/15 mm., d_{30}^{30} 0.8824, n_D^{30} 1.4931, $[\alpha]_D^{30}$ –23.0°. Alternatively, *l*-dihydro- α -curcumylamine can be treated with nitrous acid, when the resultant mixture of alcohol and hydrocarbon, after the completion of the dehydration by heating with potassium bisulphate, affords *l*- α -curcumene on distillation.

l- α -Curcumene, $C_{15}H_{22}$, b.p. 130°/13 mm., d_{20}^{20} 0.8775, n_D^{25} 1.5001, $[\alpha]_{5461}$ –41.5°, is related to cadalene (III), for *l*- α -curcumene monohydrochloride (IV), furnished this hydrocarbon on dehydrogenation with selenium. When *l*- α -curcumene was oxidised with manganese dioxide and sulphuric acid a mixture of *p*-toluic acid (V), terephthalic acid (VI), and trimellitic acid (VII), was obtained, thus proving the presence of an aromatic nucleus in the parent hydrocarbon. *l*- α -Curcumene must, therefore, possess a double bond in a side chain attached to this



nucleus. This deduction was confirmed by a careful study of products obtained by ozonolysis of *l*- α -curcumene. Acetone (from (Ia)), formaldehyde (from (Ib)), a ketone, $C_{14}H_{20}O$ ((VIII); from (Ib)), b.p. 154°/15 mm., d_{20}^{20} 0.9454, n_D^{20} 1.5016, $[\alpha]_{5461}$ –30.8° (semicarbazone, m.p. 138–139°), an acid, $C_{12}H_{16}O_2$ (IX) (from (Ia)), b.p. 180°/17 mm., $[\alpha]_{5461}$ –13.8° (in alcohol) and the corresponding aldehyde (X) (from (Ia)) (2:4-dinitrophenylhy-

drazone, m.p. 94–95°) were obtained from the oxidation products. The acid (IX), on further oxidation with potassium permanganate gave *p-tolyl methyl ketone*, *semicarbazone*, m.p. 204°.

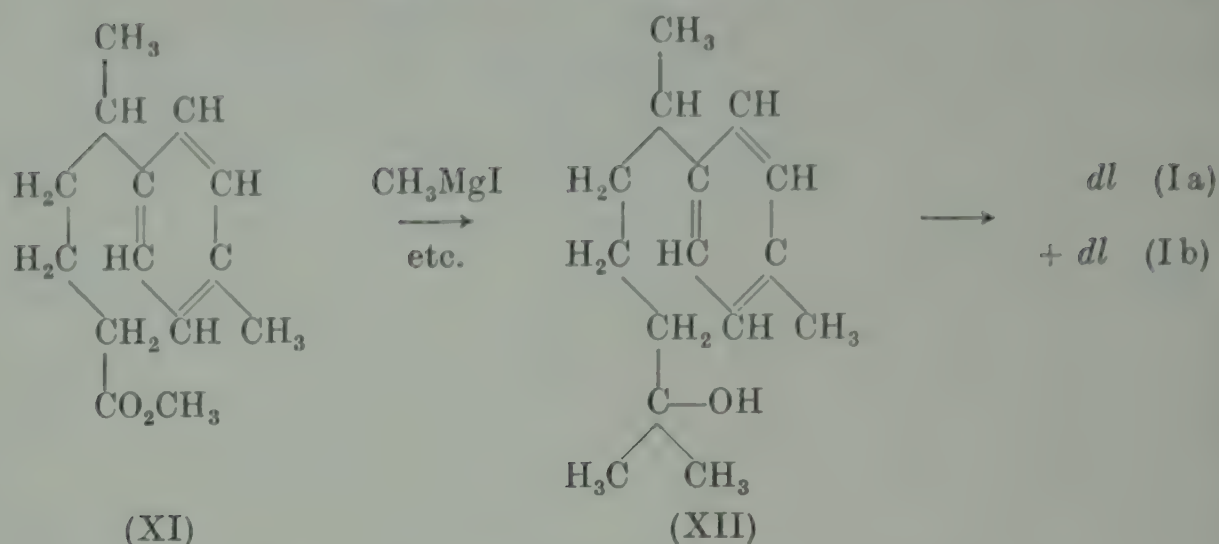


It must be concluded from the nature of these oxidation products that *l*- α -curcumene is a mixture of (Ia) and (Ib) as mentioned above.

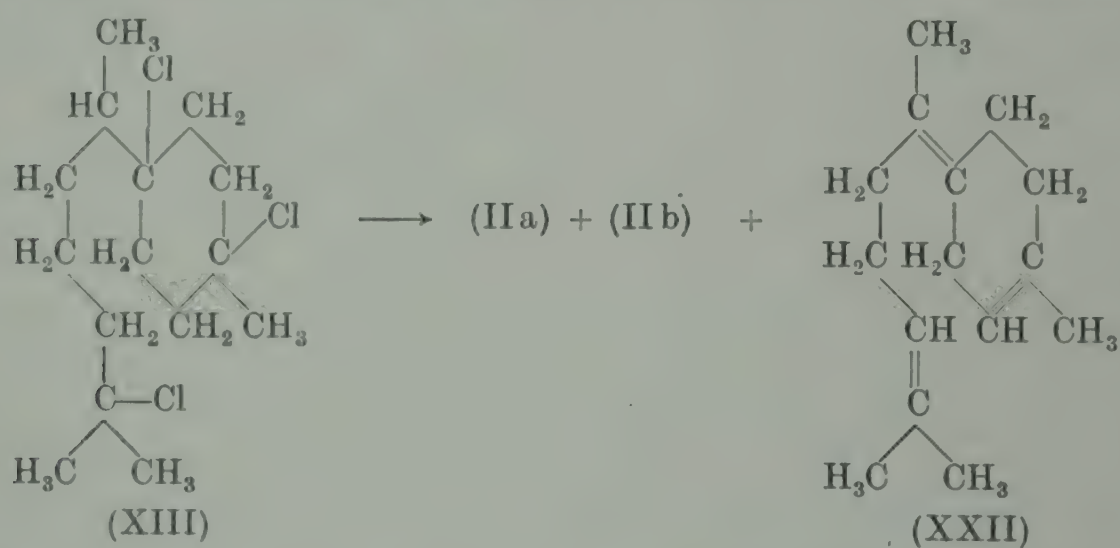
The synthesis of *dl*- α -curcumene has been described by Carter, Simonsen and Williams* who prepared it by treatment of *methyl- δ -p-tolyl-n-hexoate* (XI), with methyl magnesium iodide and dehydration of the resultant *tertiary alcohol* (XII). The physical properties of the *dl*- α -curcumene were very similar to those reported for *l*- α -curcumene and on ozonolysis acetone, formaldehyde and the *dl*-form of the ketone (VIII) were obtained.

l- β -Curcumene, $C_{15}H_{24}$, is obtained when the crystalline *tri-hydrochloride* (XIII), m.p. 84–85°, $[\alpha]_D^{30} + 26.04^\circ$ (in chloroform), is treated with sodium acetate in acetic acid solution. It boils at

* *J.C.S.* 1940, p. 451.



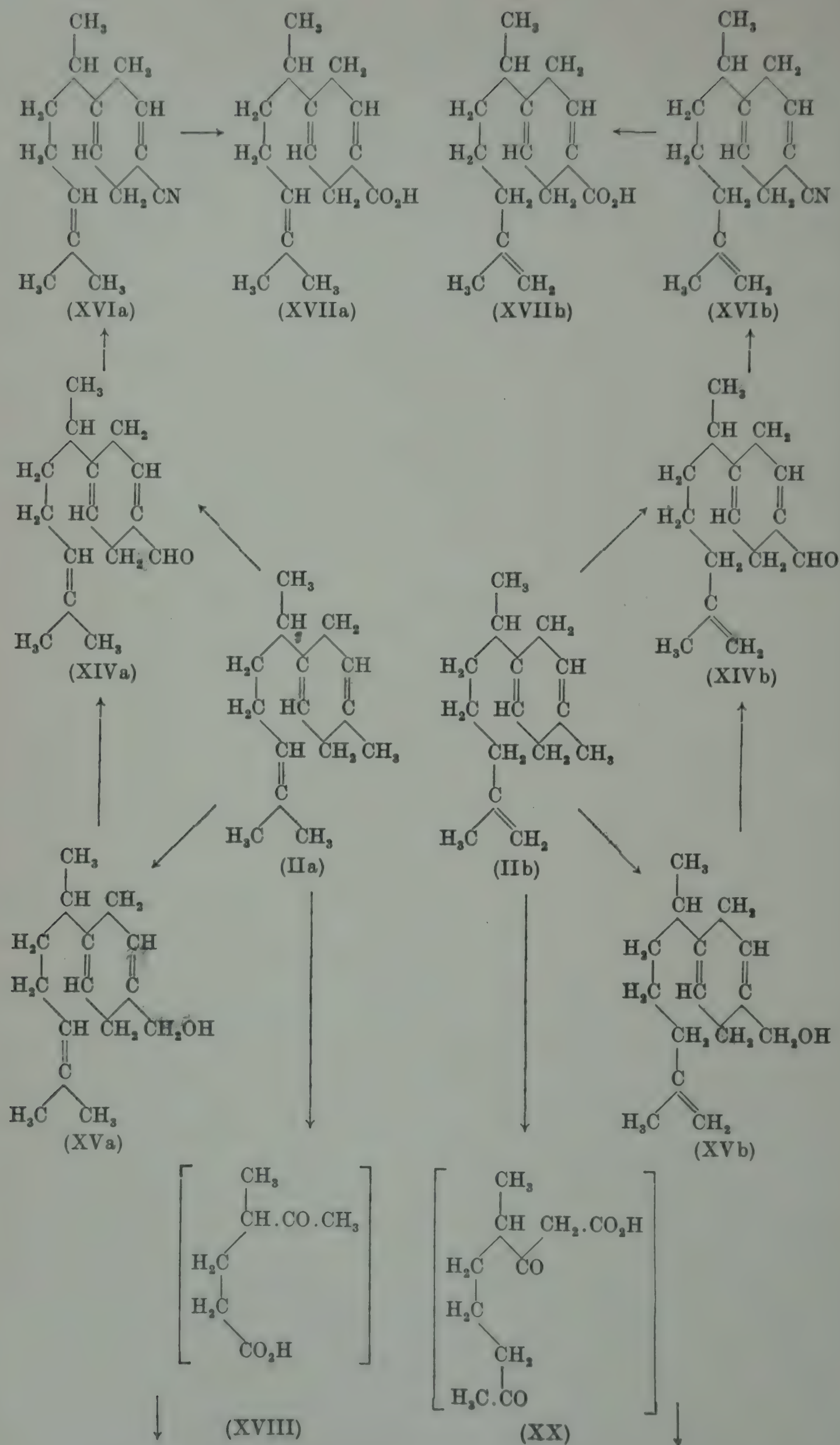
142°/19 mm., $d_{25}^{25^\circ}$ 0.8670, $n_D^{20^\circ}$ 1.491, $[\alpha]_{5461} -48.2^\circ$ and contains three ethylenic linkages. The presence of these was proved (i) by quantitative oxidation with perbenzoic acid, (ii) by titration with bromine in chloroform solution, when a liquid *hexabromide* was formed, and (iii) by catalytic hydrogenation to *hexahydro-β-curcumene*, b.p. 128°/7 mm., $d_{30}^{30^\circ}$ 0.8283, $n_D^{30^\circ}$ 1.4582, $[\alpha]_D^{30^\circ} +6.3^\circ$. From its molecular formula *l*-β-curcumene must, therefore, be monocyclic. The structure suggested for *l*-β-curcumene is not based on such firm evidence as that for *l*-α-curcumene. On

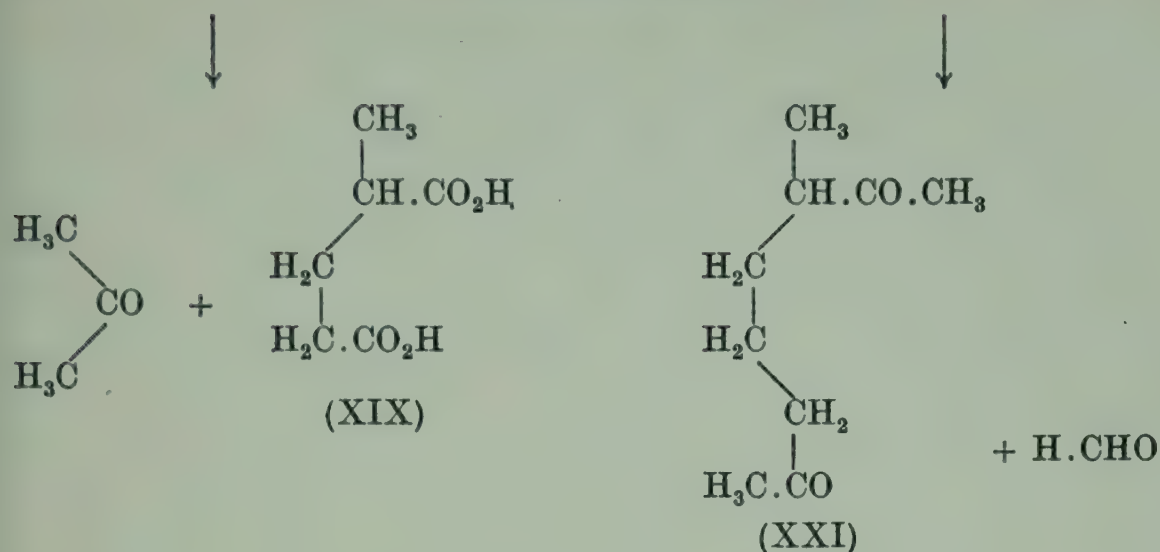


oxidation with selenium dioxide *l*-β-curcumene gave an aldehyde, *l*-β-curcumenal, C₁₅H₂₂O (XIV), b.p. 149–150°/3 mm., $d_{30}^{30^\circ}$ 0.9644, $n_D^{30^\circ}$ 1.5331, $[\alpha]_{5461} -74.1^\circ$, *oxime*, b.p. 170–175°/4 mm., $d_{30}^{30^\circ}$ 0.9851, $n_D^{30^\circ}$ 1.5324, $[\alpha]_D -67^\circ$, *semicarbazone*, m.p. 159°, $[\alpha]_D -77.8^\circ$ (in chloroform), *2:4-dinitrophenylhydrazone*, m.p. 139°, $[\alpha]_D -145.4^\circ$ (in chloroform), and a primary alcohol, *l*-β-curcumenol, C₁₅H₂₄O (XV), b.p. 175°/17 mm., $d_{30}^{30^\circ}$ 0.9563, $n_D^{30^\circ}$ 1.5164, $[\alpha]_D -39^\circ$, *p-xenylurethane*, m.p. 79–80°, isolated through its hydrogen phthalate. The presence of the aldehyde group in *l*-β-

curcumenal was proved by digesting the oxime with acetic anhydride and hydrolysing the resultant *l*- β -curcumenonitrile (XVI), b.p. 178–182°/17 mm., to the corresponding *l*- β -curcumenylic acid, C₁₅H₂₂O₂ (XVII), methyl ester, b.p. ca. 180–182°/16 mm., anilide, m.p. 87°. The relationship between *l*- β -curcumenol and *l*- β -curcumenal was demonstrated by the almost quantitative oxidation of the former to the latter by chromic acid. These experiments suggested that *l*- β -curcumene contained the group $\begin{array}{c} \text{=C—}\dot{\text{C}}\text{H}_3 \\ | \end{array}$ or >C=CH_2 as part of the ring

structure, the oxidation being analogous to that of the α - and β -pinenes to myrtenal (Vol. II, p. 140). On the assumption that one of the other ethylenic linkages was present as an isopropenyl or isopropylidene group in the side chain then, having regard to the optical activity of *l*- β -curcumene and the failure of attempts to reduce it with sodium and alcohol, the most probable formulae for *l*- β -curcumene are (IIa) and (IIb) as represented above. This view was confirmed by ozonolysis of the hydrocarbon, when acetone (from (IIa)) formaldehyde (from (IIb)), a diketone, C₉H₁₆O₂ ((XXI); from (IIb)), bis-2:4-dinitrophenylhydrazone, m.p. 178–180°, together with small amounts of levulinic acid, the ketone (VIII), the acid (IX), and the aldehyde (X), were obtained. The levulinic acid doubtless resulted from a small amount of bisabolene (XXII) (p. 22) present as impurity in the *l*- β -curcumene, and which would be expected as a by-product from the trihydrochloride (XIII). The products (VIII), (IX) and (X) were probably formed by oxidation of the cyclic portion of *l*- β -curcumene to an aromatic system, it being known that turmerone, which is closely similar, is very readily oxidised to *ar*-turmerone (see p. 202). While the diketone (XXI), formed from the easily decarboxylated and not isolated intermediate (XX), was readily obtained by ozonolysis of *l*- β -curcumene, the analogous α -methylglutaric acid (XIX), to be expected from (IIa), only resulted from an experiment in which the mixed curcumenes were ozonised and the reaction product (presumably containing (XVIII), which was not isolated) then degraded further with sodium hypobromite. The structure of *l*- α -curcumene is comparable, therefore, with that suggested for *ar*-turmerone (p. 203) and that of *l*- β -curcumene with one of the formulae proposed for turmerone



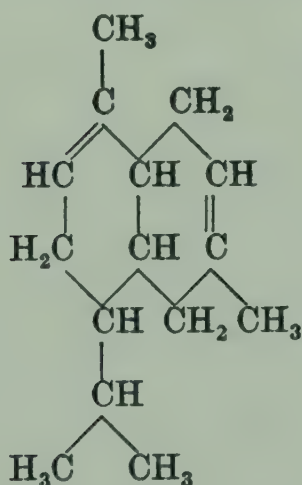


itself (p. 202). It might therefore be desirable to replace the name *l*- α -curcumene by *l*-*ar*-curcumene.

l- β -Curcumene yields a crystalline *trihydrobromide*, m.p. 73–74°. When it is warmed with dilute sulphuric acid a dicyclic sesquiterpene, b.p. 115–117°/7 mm., d_{30}^{30} 0.8932, n_D^{30} 1.4936, $[\alpha]_D^{30}$ –11.9°, of unknown structure is obtained.*

B. DICYCLIC HYDROCARBONS

CADINENE



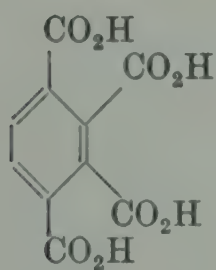
The sesquiterpene, cadinene, $\text{C}_{15}\text{H}_{24}$, has been found to occur very widely distributed in nature. It forms the main constituent of oil of cubebs (from *Piper Cubeba* L.) and it was first separated from this oil by Souberain and Capitaine,[†] who prepared from it a crystalline hydrochloride; it was studied later by a number of

* Batt and Slater (*J.C.S.* 1949, p. 838) have recently described a very closely related hydrocarbon, γ -curcumene.

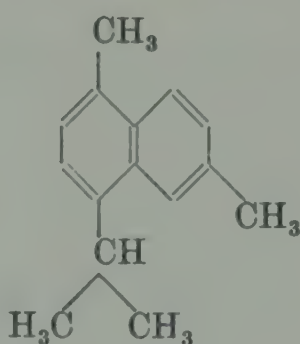
[†] *Annalen*, 1840, **34**, 323.

investigators.* It remained, however, for Wallach[†] to give it the name cadinene and to show that it occurred also in a number of other oils—galbanum oil, oil of cade, etc. He showed further that it could be obtained pure by regeneration from the hydrochloride by the action of aniline.

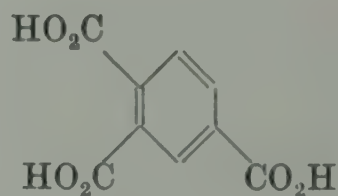
Although the formation of a crystalline dihydrochloride and the physical constants of the hydrocarbon[‡] showed the presence of two ethylenic linkages, and tentative formulae were suggested by Semmler,[§] no direct evidence as to its constitution was available prior to the researches of Ruzicka and his collaborators. The early attempts at degradative oxidation met with little success. Wallach^{||} found that with chromic acid only fatty acids were obtained, whilst Semmler and Jonas[¶] could obtain no well-characterised derivatives on ozonolysis. In 1923 Ruzicka, Schinz and Meyer^{**} observed that, when the hydrocarbon was oxidised with manganese dioxide and sulphuric acid, *mellophanic acid* (II) and *trimellitic acid* (III), together with benzene pentacarboxylic acid, were formed. The latter acid resulted evidently from some secondary reaction. Of greater interest, however, was the discovery by Ruzicka and Meyer^{††} that, on dehydrogenation, cadinene gave cadalene (I). The nature of the carbon skeleton in cadinene was thus established and it only remained to determine



(II)



(I)



(III)

* *Inter al.* Gerhardt, *Traité*, 1854, III, 634; Lallemand, *Annalen*, 1860, 114, 193; Berthelot, *Bull. Soc. chim.* 1869 [ii], 11, 30; Schmidt, *Arch. Pharm.* 1870, 191, 32; Ogialoro, *Gazzetta*, 1875, 5, 467; Gladstone and Dale, *Phil. Trans.* 1863, p. 317; *J.C.S.* 1867, 20, 1. The relationship of the sesquiterpene, *kiganene*, isolated by Kimura and Mizoshita (*Mem. Coll. Sci. Kyoto*, 1931, A 14, 273) from the wood oil of *Cryptomeria japonica*, to cadinene is uncertain, but it is said to afford cadinene dihydrochloride on treatment with hydrogen chloride.

† *Annalen*, 1887, 238, 78.

‡ Brühl, *Ber.* 1888, 21, 163.

§ *Die Ätherischen Öle*, II, 563; *Ber.* 1914, 47, 2558.

|| *Annalen*, 1887, 238, 87.

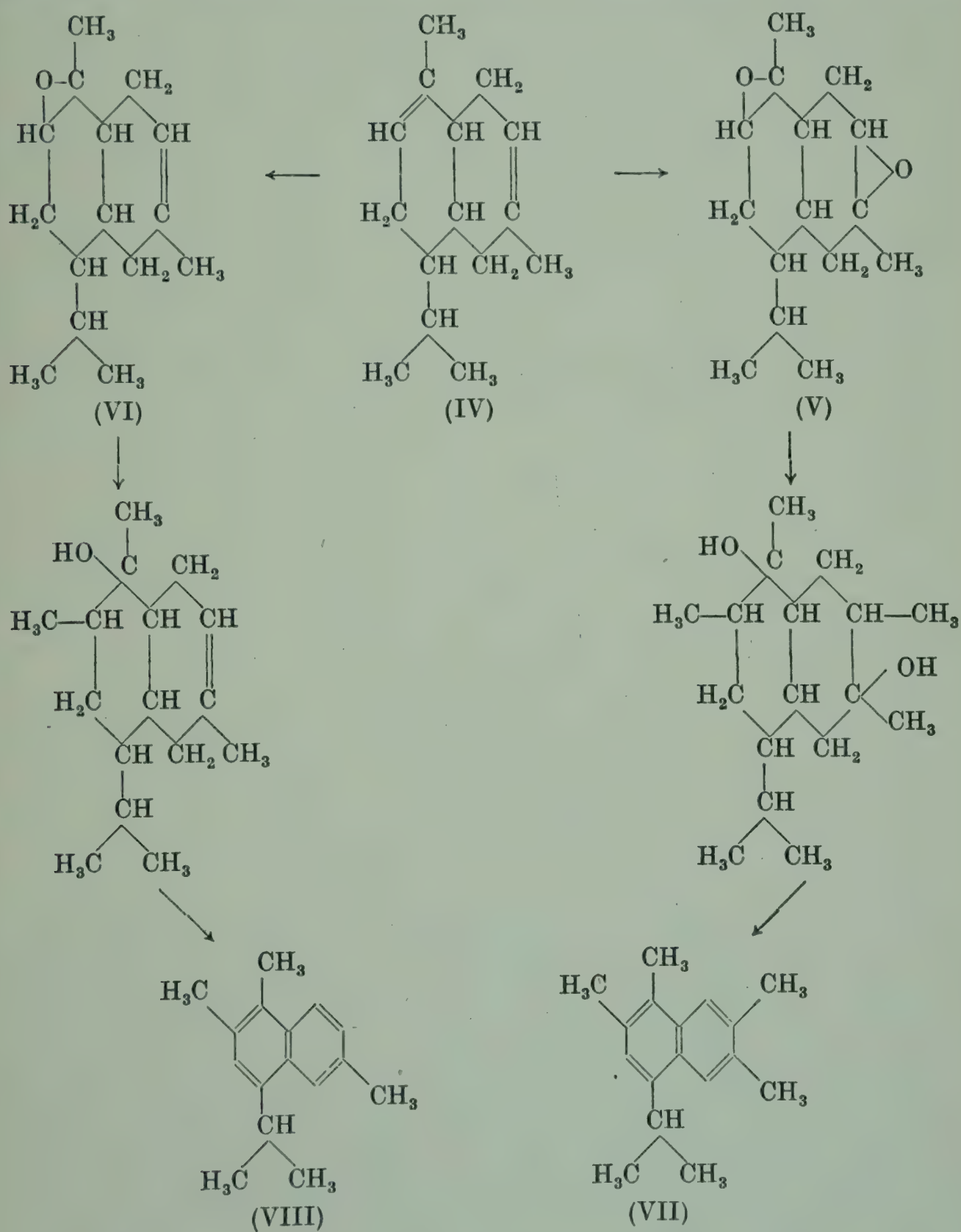
¶ *Ber.* 1914, 47, 2078.

** *Helv. Chim. Acta*, 1923, 6, 1077.

†† *Ibid.* 1921, 4, 505; compare Ruzicka, Meyer and Mingazzini, *ibid.* 1922, 5, 357.

the position of the two ethylenic linkages in the hexahydrocadalene.

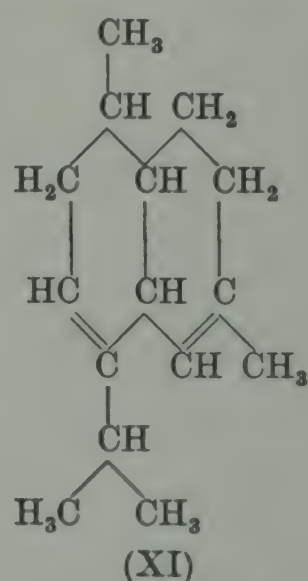
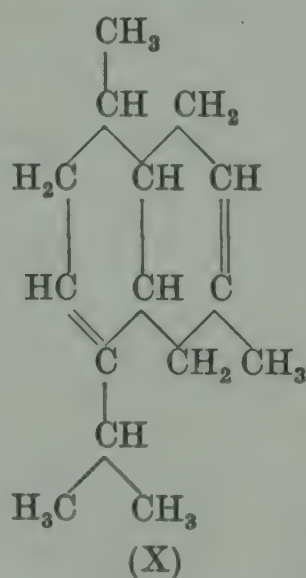
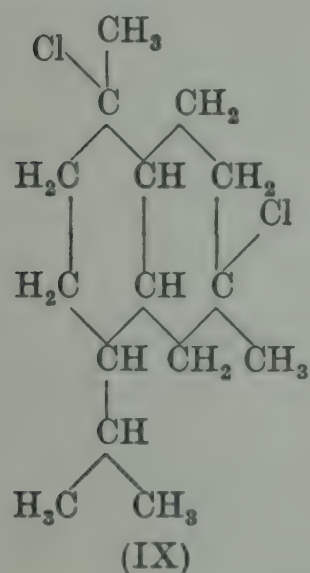
The structure of cadinene has been established by the elegant experiments of Campbell and Soffer,* who have shown it to be represented by (IV). Cadinene, $C_{15}H_{24}$, afforded a *dioxide*, $C_{15}H_{24}O_2$ (V), b.p. $68-73^\circ$ (bath temperature)/0.0002 mm., on prolonged treatment with excess of perbenzoic acid in cold



* *J. Amer. C.S.* 1942, 64, 417.

chloroform solution. The use of only one molecular proportion of the perbenzoic acid gave in a short time an excellent yield of the *monoxide*, $C_{15}H_{24}O$ (VI), b.p. $91-119^{\circ}/0.3$ mm., of cadinene. Both the dioxide and the monoxide were treated with excess of methyl magnesium iodide and the resulting tertiary alcohols dehydrogenated with selenium to give 4-isopropyl-1:2:6:7-tetramethylnaphthalene (VII), m.p. $102-103^{\circ}$, *picrate*, m.p. 145° and 4-isopropyl-1:2:6-trimethylnaphthalene (VIII), b.p. $157-162^{\circ}/12$ mm., *picrate*, m.p. $142.5-143^{\circ}$, *trinitrobenzoate*, m.p. $167.5-168^{\circ}$, *styphnate*, m.p. $170-170.5^{\circ}$ respectively. The formation of these hydrocarbons proves unambiguously the positions of the ethylenic linkages indicated in (IV), so that cadinene dihydrochloride must be represented by (IX).

The formulae (X) and (XI), previously proposed for cadinene by Ruzicka and Stoll,* were based on the results of their ozonolysis experiments and on the observation by Semmler and Stenzel† that *copaene* (see p. 88) gave cadinene dihydrochloride on treatment with hydrogen chloride. Semmler and Stenzel had



found that oxidative degradation of *copaene* indicated the double bond in this hydrocarbon to be adjacent to an *isopropyl* group, as in formulae (X) and (XI), but this is now known to be incorrect. Ruzicka and Stoll, on ozonolysis of cadinene, obtained a mixture of acids, which, on esterification, gave a *diethyl ester* having the composition $C_{19}H_{30}O_5$, or $C_{19}H_{32}O_5$, corresponding to an *acid*, $C_{15}H_{22}O_5$ or $C_{15}H_{24}O_5$, thus showing the absence of exocyclic methylene groups in the parent cadinene.

* *Helv. Chim. Acta*, 1924, 7, 86.

† *Ber.* 1914, 47, 2560.

The acid obtained on ozonolysis had, moreover, as its composition shows, been formed from a precursor by loss of water. This is analogous to the change observed by Harries and Adams in the oxidation of limonene (Vol. I, p. 154) and the dibasic acid obtained from cadinene was represented therefore as (XII) or (XIII) (p. 30). Clearly the experiments of Ruzicka and Stoll showed that the two double bonds of cadinene could not be in the same ring, but it is quite possible to reconcile their results with the formula (IV) now accepted for cadinene, when the formulae (XII) or (XIII), for the acid obtained on ozonolysis, would become (XIV a) or (XIV b). In actual fact the formula (X), previously proposed for cadinene, has recently been shown* to represent *isozingiberene* (see p. 16).

Cadinene has not been prepared synthetically. It can be identified by the preparation of the *dihydrochloride*, m.p. 117–118°, $[\alpha]_D - 36.24^\circ$. The hydrocarbon is a somewhat viscid colourless oil and, when purified through its dihydrochloride, has b.p. 134–136°/11 mm., $d_4^{20^\circ} 0.9189$, $n_D^{20^\circ} 1.5079$, $[\alpha]_{5461} - 125.2^\circ$;† for the dextrorotatory hydrocarbon from West Indian sandalwood oil, Deussen‡ gives the values b.p. 138–140°/13 mm., $d^{16^\circ} 0.9260$, $n_D^{16^\circ} 1.5093$, $\alpha_D + 38.72^\circ$. Cadinene is extremely stable and when heated under pressure at 330° is not altered.§

Cadinene cannot be reduced with sodium in alcoholic solution, but with hydriodic acid and red phosphorus it gave a hydrocarbon, b.p. 270–275°/750 mm., $d^{18^\circ} 0.872$, $n_D 1.4743$, which has not been identified.|| On catalytic hydrogenation in the presence of platinum, *tetrahydrocadinene*, $C_{15}H_{28}$, b.p. 125–128°/10 mm., $d^{20^\circ} 0.8838$, $n_D^{20^\circ} 1.4804$, $\alpha_D - 20^\circ$, was obtained.¶ It is interesting to note that *d*-cadinene also yielded a laevorotatory tetrahydrocadinene, b.p. 135–137°/14 mm., $d^{16^\circ} 0.8873$, $n_D^{16^\circ} 1.4815$, $\alpha_D - 10.07^\circ$.** Tetrahydrocadinene can be prepared also by the reduction of cadinene dihydrochloride. Cadinene on dehydrogenation with sulphur yields cadalene (see above) and this change

* Soffer, Steinhardt, Turner and Stebbins, *J. Amer. C.S.* 1944, **66**, 1520.

† Henderson and Robertson, *J.C.S.* 1924, **125**, 1992.

‡ *J. pr. Chem.* 1928 [ii], **120**, 121.

§ Semmler and Jakubowicz, *Ber.* 1914, **47**, 2258.

|| Wallach and Walker, *Annalen*, 1887, **238**, 80.

¶ Semmler and Jonas, *Ber.* 1914, **47**, 2071; Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, **5**, 357.

** Deussen and Awramoff, *J. pr. Chem.* 1928 [ii], **120**, 121.

can be effected also with selenium* or with platinum at 300–310°.[†]

No experiments have been reported on the oxidation of cadinene with potassium permanganate and reference has been made already to the results obtained on ozonolysis. With chromyl chloride, it yields an additive compound having the composition $C_{15}H_{24}$, $2\frac{1}{2}CrO_2Cl_2$, which, on decomposition with water, yields a liquid acid and a neutral oil.[‡]

Cadinene reacts very readily with the halogens, but no crystalline derivative has been prepared. The dihydrochloride is obtained when the hydrocarbon is treated with hydrogen chloride in either ethereal or acetic acid solution and, since cadinene can be regenerated from it by the action of either sodium acetate or aniline, its preparation affords a convenient method for the purification of the sesquiterpene. When the dihydrochloride was treated with magnesium it yielded a hydrocarbon, $C_{15}H_{26}$, b.p. 130–135°/11 mm., d 0.9083, together with impure cadinene.[§] By the action of silver acetate on the dihydrochloride Henderson and Robertson^{||} prepared *cadinene glycol*, m.p. 194–195°, a small quantity of a tertiary alcohol, probably cadinol, being formed simultaneously.

Cadinene dihydrobromide melts at 124–125°, $[\alpha]_D - 36.13^\circ$, and the *dihydriodide* at 105–106°, $[\alpha]_D - 48^\circ$.[¶]

Although cadinene is not altered when digested with sulphuric acid in alcohol solution (10 per cent.),^{**} it is isomerised when treated with the Bertram-Walbaum mixture, with acetic acid at 230–235° under pressure or with formic acid at 100°.^{††} The hydrocarbon, *isocadinene*, obtained in these reactions, has been investigated by Henderson and Robertson,^{‡‡} and has been found to be identical with that isolated by Tröger and Feldmann,^{§§} and Lepeschkin^{|||} from oil of cade, which was later prepared

* Diels and Karstens, *Ber.* 1927, **60**, 2325.

† Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 90.

‡ Gibson, Robertson and Sword, *J.C.S.* 1926, p. 164.

§ Deussen *et al.*, *J. pr. Chem.* 1927 [ii], **117**, 303.

|| *J.C.S.* 1924, **125**, 1992.

¶ Wallach, *Annalen*, 1887, **238**, 151.

** Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 92.

†† Henderson and Robertson, *J.C.S.* 1924, **125**, 1992; Robertson, Kerr and Henderson, *ibid.* 1925, **126**, 1946.

‡‡ *Ibid.* 1926, p. 2811.

§§ *Arch. Pharm.* 1898, **236**, 692.

||| *J. Russ. Phys. Chem. Soc.* 1908, **40**, 726.

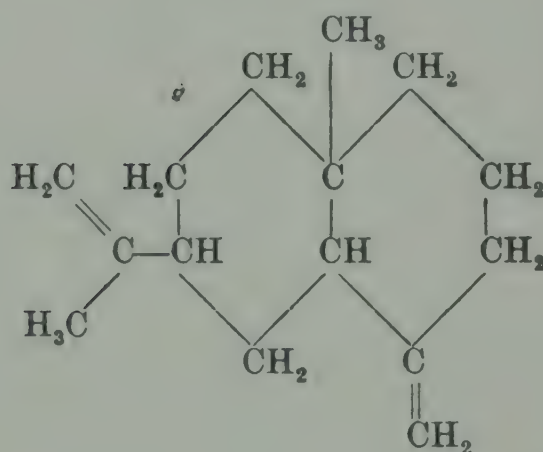
synthetically by Ruzicka and Capato* from nerolidol and bisabolene (p. 126). The identity of the three hydrocarbons is shown by a comparison of their constants:

	b.p./11–12 mm.	d^{20}_D	n^{20}_D
<i>iso</i> Cadinene	124–126°	0.914	1.515
Cade oil sesquiterpene	124–128°	0.918	1.515
Synthetic terpene	125–126°	0.916	1.509

*iso*Cadinene differs from cadinene in that it does not yield a crystalline hydrochloride, but it is a hexahydrocadalene, since on dehydrogenation cadalene is obtained.† Although Robertson and Henderson regarded *isocadinene* as a chemical individual it has recently been shown by Gillam, Moss and West‡ to be inhomogeneous.

Cadinene *nitrosochloride*, m.p. 93–94°, and *nitrosate*, m.p. 105–110°, have been described by Schreiner and Kremers§.

SELINENE



In 1897 Ciamician and Silber^{||} observed that celery oil (from the fruit of *Apium graveolens*) contained a sesquiterpene, $C_{15}H_{24}$, which was later characterised by Schimmel and Co.[¶] by the preparation of a crystalline *dihydrochloride*, m.p. 72–74°, and given the name selinene. Valuable additions to our knowledge of the hydrocarbon resulted from the investigations of Semmler and

* *Helv. Chim. Acta*, 1925, 8, 259.

† Compare Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

‡ *J.C.S.* 1948, p. 1306.

§ *Pharm. Arch.* 1899, 2, 300.

^{||} *Ber.* 1897, 30, 496.

¶ *Schimmel's Report*, 1910, April, p. 95.

Risse.* They were able to confirm Schimmel and Co.'s observation, that the natural hydrocarbon and that regenerated from the dihydrochloride differed in their physical properties, and they designated the former β -selinene and the latter α -selinene.

	B.P.	d^{20°	$n_D^{20^\circ}$	α_D
β -Selinene	136–139/17 mm.	0.9107	1.50311	+31.36°
α -Selinene	128–132/11 mm.	0.9190	1.50920	+61.36°

The molecular refraction (66.28) of the two hydrocarbons indicated that they were dicyclic and contained two ethylenic linkages. This was confirmed by the reduction of the dihydrochloride with sodium in alcoholic solution to *tetrahydroselinene*, $C_{15}H_{28}$, b.p. 125–126°/10 mm., d^{20° 0.8889, n_D 1.48375, α_D +1.12°, the same hydrocarbon being obtained by the catalytic hydrogenation of selinene.

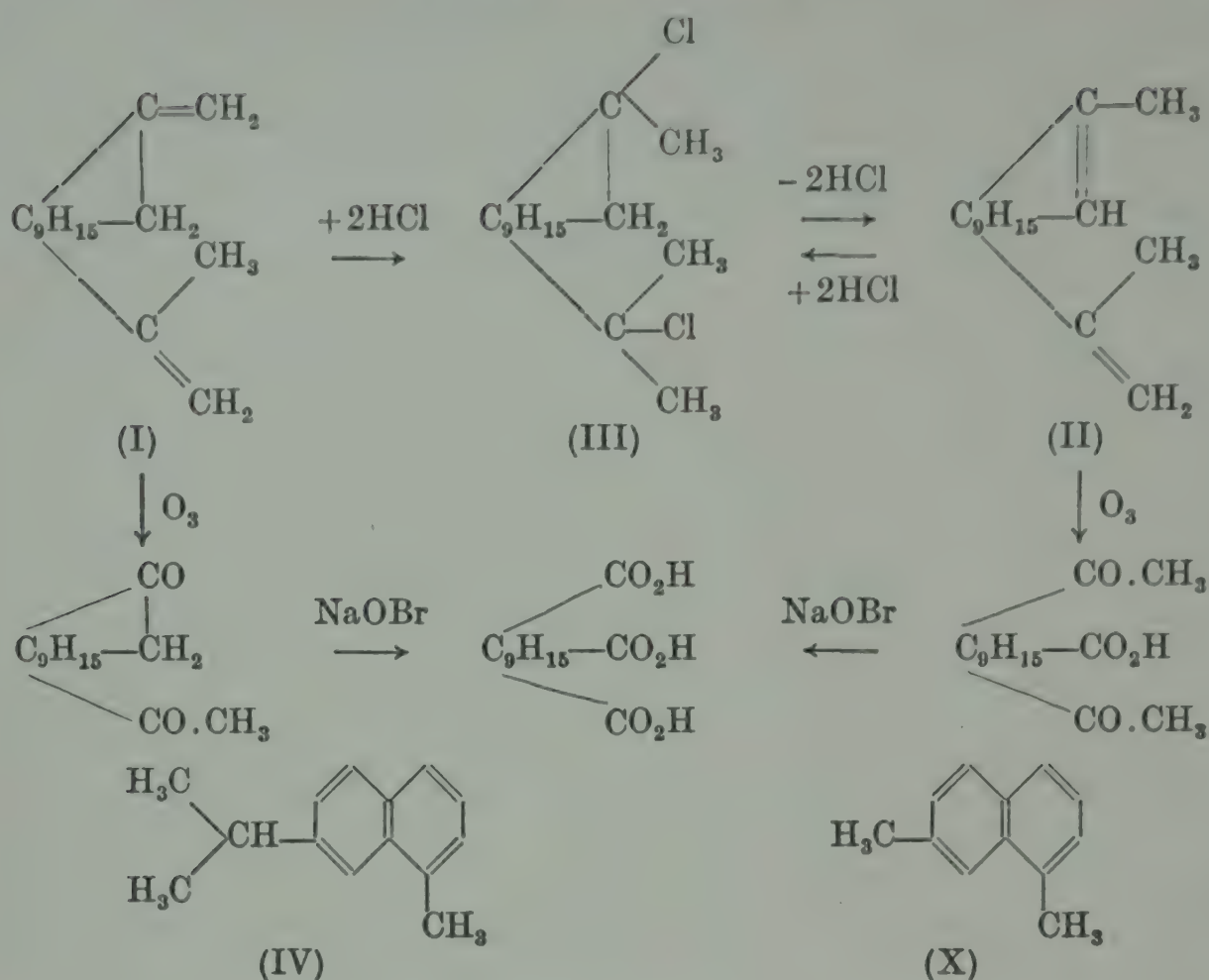
The difference in the physical properties of α - and β -selinene was due evidently to a difference in structure, and this was confirmed by a study of the products formed on ozonolysis. When β -selinene (natural selinene) was oxidised with ozone it gave a *diketone*, $C_{13}H_{20}O_2$, which after purification through its *disemicarbazone*, m.p. 222°, had b.p. 123–125°/0.2 mm., $d_4^{19^\circ}$ 1.0575, $n_D^{19^\circ}$ 1.4999. This, on further oxidation with sodium hypobromite, yielded a tricarboxylic acid, $C_{12}H_{18}O_6$, m.p. 188°. α -Selinene, on the other hand, gave a *diketonic monobasic acid*, $C_{14}H_{22}O_4$, which was purified through its *methyl ester*, $C_{15}H_{24}O_4$, b.p. 185–190°/11 mm., d^{20° 1.0635, n_D 1.4788, α_D +4.24°. This diketonic acid gave on oxidation with sodium hypobromite the same tricarboxylic acid, m.p. 188°, as had been prepared from β -selinene.

It was pointed out by Ruzicka and Stoll† that these results can be simply explained if it be assumed that in β -selinene (I) there is an exocyclic ethylenic linkage, which becomes endocyclic in the formation of α -selinene (II) by the elimination of hydrogen chloride from the dihydrochloride (III).

Whilst Semmler and Risse's experiments established the nature of the ethylenic linkages in α - and β -selinene and showed

* Ber. 1912, 45, 3301, 3725; 1913, 46, 599. The natural hydrocarbon found by Baker and Smith (*J. Proc. Roy. Soc. New South Wales*, 1911, 42, 157; compare Semmler and Tobias, Ber. 1913, 46, 2029; Semmler and Risse, *ibid.* 2303) in many eucalyptus oils, to which the name *eudesmene* was given, must be identical with one of the selinenes but its constitution has not been determined (compare Ruzicka, Wind and Koolhaas, *Helv. Chim. Acta*, 1931, 14, 1138 footnote).

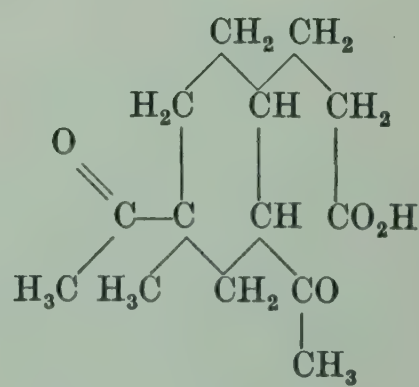
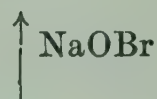
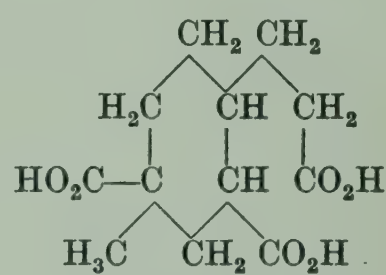
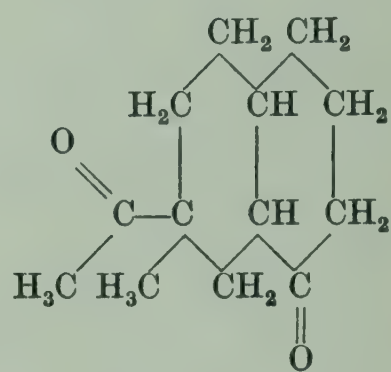
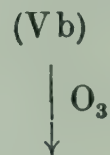
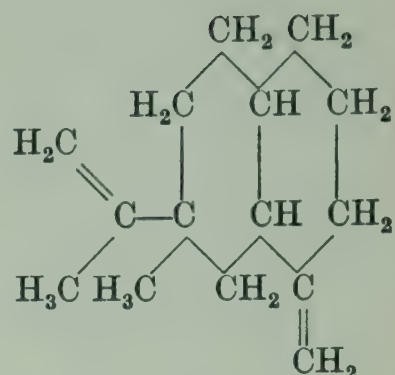
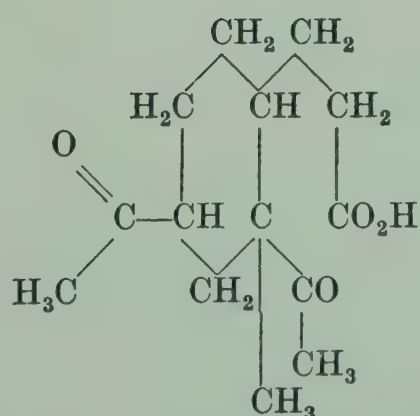
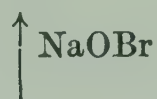
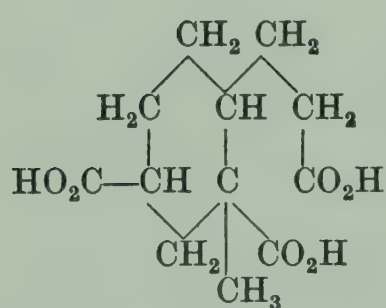
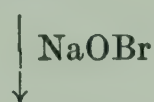
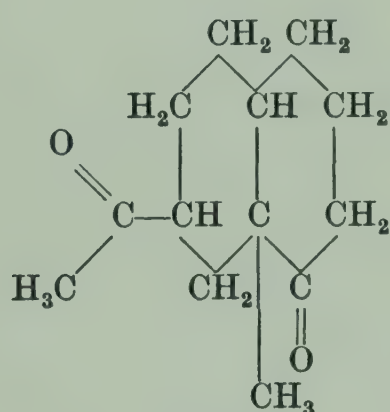
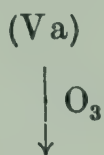
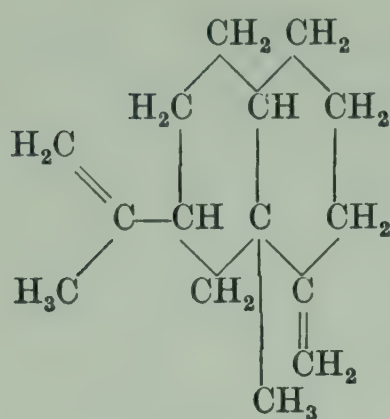
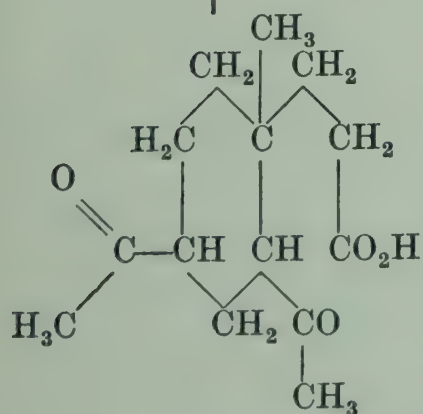
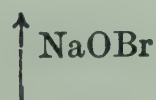
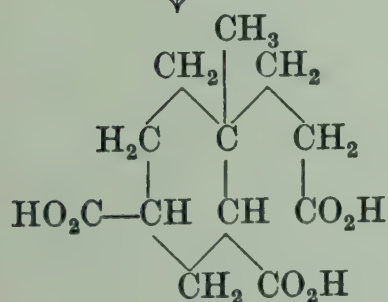
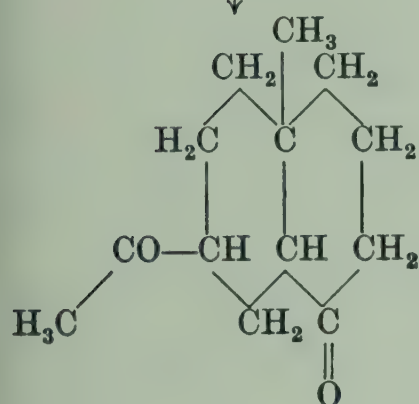
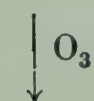
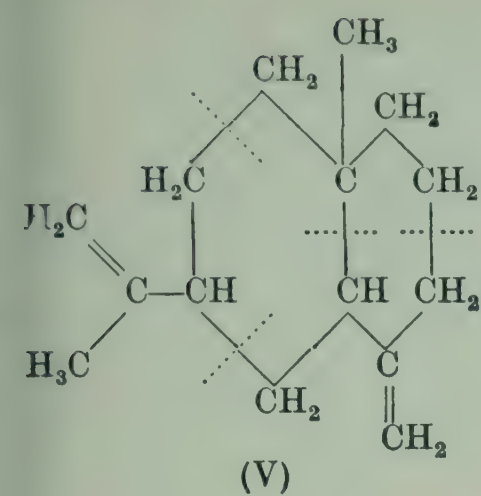
† *Helv. Chim. Acta*, 1922, 5, 926.

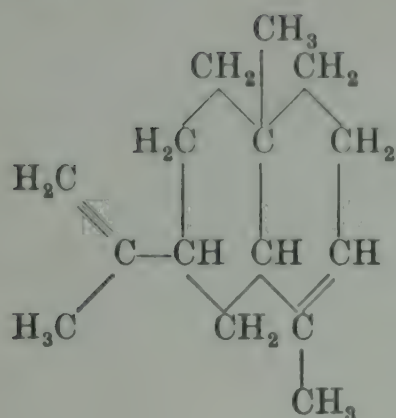


the relationship of the selinenes to one another, they afforded no evidence of the ring structure of the two hydrocarbons and the formulae advanced by them had no experimental basis and were purely hypothetical. Of fundamental importance therefore was the observation of Ruzicka, Meyer and Mingazzini* that β -selinene on dehydrogenation with sulphur gave *eudalene* (IV). This hydrocarbon is also obtained together with tetrahydro-selinene when selinene is heated with palladised charcoal.[†] The formation of eudalene, if considered in conjunction with the ozonolysis products referred to above, showed that β -selinene must be represented by either (V), (Va) or (Vb) and α -selinene by (VI), (VIa) or (VIb). Of these formulae (Vb) and (VIb) are extremely improbable, since assuming them to be correct, on dehydrogenation the formation of 2:8-dimethylnaphthalene (X) would be anticipated. A consideration of the alternative formulae (V) and (Va) for β -selinene and of (VI) and (VIa) for α -selinene, shows that (V) and (VI) are most probably correct, since they can be built up from three isoprene nuclei as indicated by the dotted lines in (V).

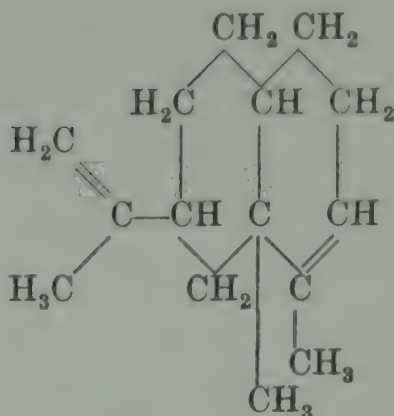
* *Helv. Chim. Acta*, 1922, 5, 363.

† Linstead, Michaelis and Thomas, *J.C.S.* 1940, p. 1139.

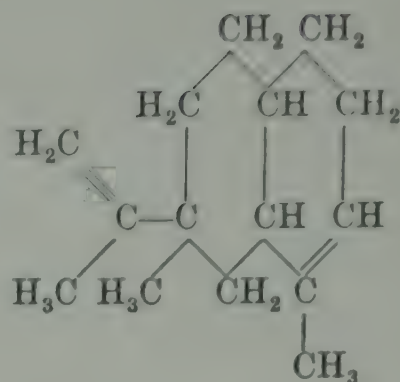




(VI)



(VIa)



(VIb)

Indirect proof of this was obtained by Ruzicka and Stoll.* If either formulae (V), (V a) or (V b) correctly represents β -selinene, then the tricarboxylic acid (*v. supra*) must be either (IX), (IX a) or (IX b). If these formulae for the tricarboxylic acid be inspected, it will be observed that in both (IX a) and (IX b) one of the carboxyl groups is tertiary and should therefore, as is the case with camphoric acid (Vol. II, p. 485), give rise to a hydrogen ester on esterification. Ruzicka and Stoll found, however, that, on esterification, a neutral *triethyl ester*, b.p. $170^{\circ}/0.2$ mm., was obtained, and that this was completely hydrolysed by alkali under conditions which gave with ethyl camphorate the hydrogen ester. It may therefore be assumed with some degree of certainty that β -selinene has formula (V), and α -selinene (VI), the related oxidation products being represented by (VII), (VIII) and (IX).

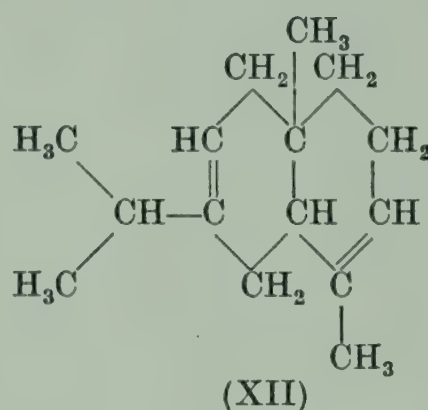
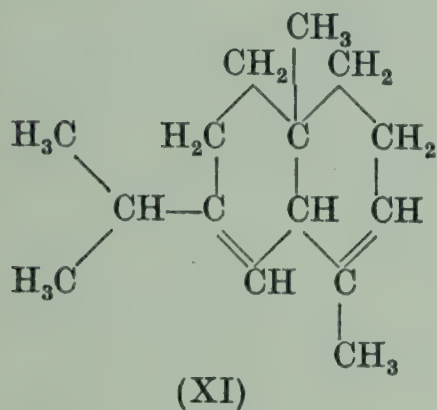
Both α - and β -selinenes can be characterised by the preparation of the *dihydrochloride*, m.p. $72-74^{\circ}$, $[\alpha]_D + 18^{\circ}$, although according to Ruzicka, Wind and Koolhaas[†] the hydrochloride, when freshly prepared, has m.p. 52° , $[\alpha]_D - 70^{\circ}$ (in chloroform). On keeping for some years this changes into the higher melting hydrochloride. If the dihydrochloride is heated with milk of lime at 95° it yields *selinenol* or α -*eudesmol*, m.p. $78-79^{\circ}$, $[\alpha]_D + 38^{\circ}$ (in chloroform) (see p. 145). This on catalytic hydrogenation gives *dihydroselenenol* or *dihydroeudesmol*, $C_{15}H_{28}O$, m.p. $85-86^{\circ}$, $[\alpha]_D + 17^{\circ}$ (in chloroform) (see p. 150). Ruzicka and Stoll[‡] have observed the presence in celery oil of a sesquiterpene alcohol or mixture of alcohols, but these do not appear to be identical with selinenol, since they do not yield selinene dihydrochloride when treated with hydrogen chloride.

* *Helv. Chim. Acta*, 1923, 6, 846.

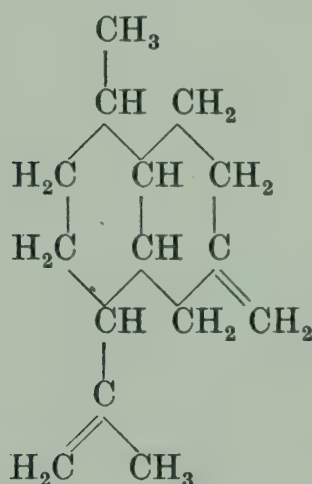
† *Ibid.* 1931, 14, 1132.

‡ *Ibid.* 1923, 6, 852.

Like dipentene, with which it is structurally closely related, α -selinene can be readily isomerised by digestion with sulphuric acid in alcoholic solution, a *hydrocarbon*, b.p. $130^\circ/12$ mm., $d_4^{14^\circ}$ 0.9234, $n_D^{14^\circ}$ 1.5167, $\alpha_D + 194.3^\circ$, being formed, which no longer gives a crystalline hydrochloride. This hydrocarbon is probably represented by either δ -selinene (XI) or ϵ -selinene (XII). The ethylenic linkages cannot be conjugated, since it was not reduced by sodium in alcoholic solution.



SESQUIBENIHENE

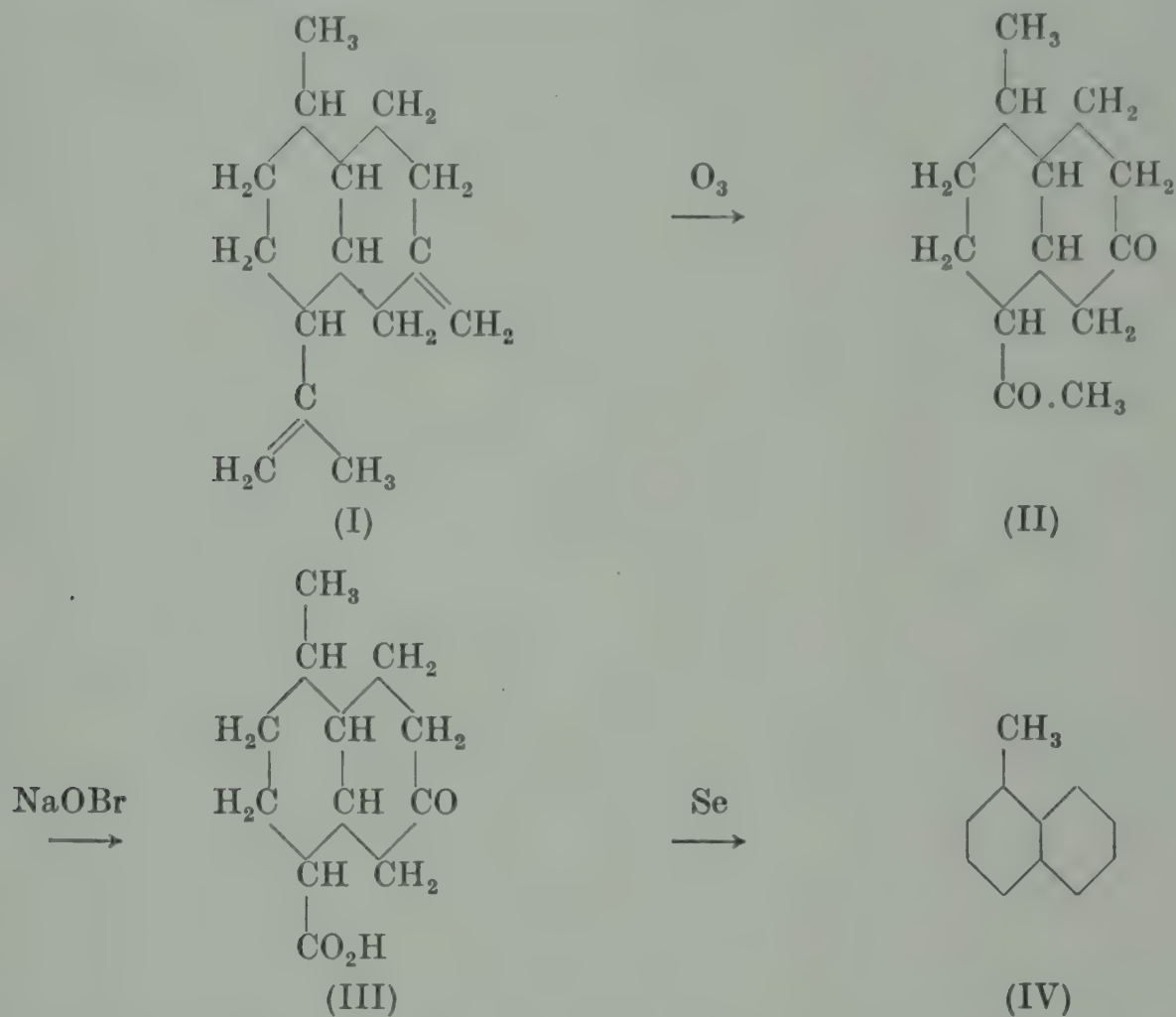


The hydrocarbon, *sesquibenihe*, $C_{15}H_{24}$, b.p. $130^\circ/10$ mm., $d_4^{29^\circ}$ 0.956, $n_D^{29^\circ}$ 1.5033, $[\alpha]_D^{29^\circ} - 4.1^\circ$, has been shown by Katsura* to be present in the essential oil from *Chamaecyparis formosensis*.

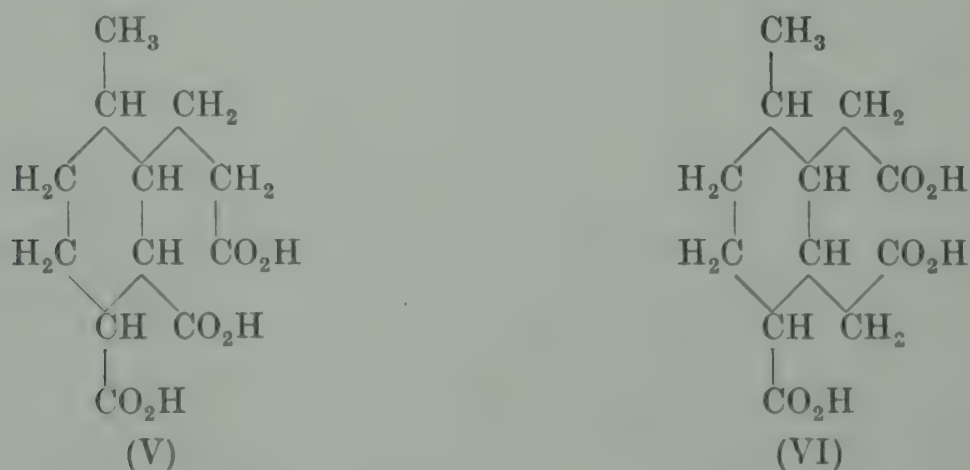
The structure (I), which has been assigned to the hydrocarbon is based on the following evidence. It contains two ethylenic linkages since on catalytic hydrogenation it yielded *tetrahydro-sesquibenihe*, $C_{15}H_{28}$, b.p. $127-128^\circ/10$ mm., $d_4^{33^\circ}$ 0.8866, $n_D^{33^\circ}$ 1.479, $[\alpha]_D^{33^\circ} - 0.64^\circ$. On ozonolysis it gave formaldehyde and a diketone, $C_{13}H_{20}O_2$ (II), b.p. $175-185^\circ/12$ mm., from which by

* *J.C.S. Japan*, 1942, **63**, 1470.

the action of cold sodium hypobromite solution a *keto-acid*, $C_{12}H_{18}O_3$, was obtained which must be represented by (III) since after reduction with sodium it gave on dehydrogenation with selenium 1-methylnaphthalene (IV).



If the diketone (II) was oxidised with warm sodium hypobromite solution then, in place of the keto-acid (III), a *tricarboxylic acid*, $C_{12}H_{18}O_6$, was obtained which may be represented by either (V) or (VI).



THE CARYOPHYLLENES

The mixture of hydrocarbons, known as the caryophyllenes, forms the main hydrocarbon constituent of oil of cloves (from *Eugenia caryophyllata*) and it occurs also in African copaiba oil (from *Oxystigma Mannii* Harms), in French lavender oil* and in the oil from *Pinus maritima*.† Recently Naves‡ has made the important observation that caryophyllene does not seem to be present in the benzene extract of cloves, but instead an oxygenated precursor identical with the caryophyllene oxide, m.p. 63–64°, of Treibs (see p. 61) was isolated. Apparently the caryophyllene is formed from this precursor during steam distillation.

The presence in clove oil of a hydrocarbon having a high boiling-point was first observed by Ettling§ and this was confirmed by other investigators.¶ Church¶ was, however, the first to show it to have the composition $C_{15}H_{24}$, and Brühl** from a consideration of its physical constants, suggested that it was a dicyclic hydrocarbon containing two ethylenic linkages. A more detailed study of the sesquiterpene was made by Wallach and Walker,†† who prepared a number of crystalline derivatives and showed that the hydrocarbons present in oil of cloves and copaiba** oil were identical.

Although caryophyllene§§ can be characterised by the preparation of a number of crystalline derivatives, it is not a homogeneous substance. This was first recognised by Deussen||| and it is necessary to consider first the evidence on which this is based.

Wallach and Walker,¶¶ and Kremers and Schreiner*** had prepared from caryophyllene a *nitrosochloride*, m.p. 161–163°, which

* Seidel, Müller and Schinz, *Helv. Chim. Acta*, 1944, **27**, 738.

† Dupont, Dulou and Naffa, *Bull. Soc. chim.* 1948 [v], **15**, 990.

‡ *Helv. Chim. Acta*, 1948, **31**, 378. § *Annalen*, 1834, **9**, 68.

¶ Böckmann, *Annalen*, 1838, **27**, 105; Bruning, *ibid.* 1857, **104**, 202; Williams, *ibid.* 1858, **107**, 242.

¶ *J.C.S.* 1875, **28**, 113.

** *Ber.* 1888, **21**, 163.

†† *Annalen*, 1892, **271**, 288.

** Compare Blanchet, *Annalen*, 1833, **7**, 156; Souberain and Capitaine, *ibid.* 1840, **34**, 321; Posselt, *ibid.* 1849, **69**, 67; Strauss, *ibid.* 1868, **148**, 148; Levy and Engländer, *ibid.* 1887, **242**, 189; *Ber.* 1885, **18**, 3206.

§§ The term caryophyllene is used here to designate the mixture of hydrocarbons having the composition $C_{15}H_{24}$, which occurs in oil of cloves.

||| *Annalen*, 1907, **356**, 1.

¶¶ *Ibid.* 1892, **271**, 288.

*** *Pharm. Arch.* 1899, **2**, 293.

they characterised by the preparation of two *nitrolbenzylamines*, m.p. 167° and 128°, and a *nitrolpiperidide*, m.p. 145–146°. They described also a blue caryophyllene *nitrosite*, which was dextro-rotatory and which isomerised on exposure to light, the substance obtained depending upon the nature of the solvent used. A *nitrosate*, m.p. 148–149°, * 159°, † was prepared also.

A prolonged series of investigations led Deussen‡ to conclude that caryophyllene contains two and very probably three hydrocarbons— α -caryophyllene, β -caryophyllene and γ -caryophyllene or *isocaryophyllene*. Whilst the presence of the two former hydrocarbons in the oil is regarded as established, it does not appear to be quite definitely proved that γ -caryophyllene is not formed during the process involved in its isolation. Only a very partial separation of the sesquiterpenes can be effected by fractional distillation and only γ -caryophyllene has been obtained pure, although the experiments of Ruzicka and Wind§ render its homogeneity somewhat doubtful. Before proceeding to consider the structure of the caryophyllenes, it will be convenient to discuss the evidence which Deussen advanced for their individual existence.

α -Caryophyllene.|| This hydrocarbon, which is optically inactive, is present in the highest boiling sesquiterpene fraction, b.p. 132–134°/16 mm., $\alpha_D - 4.22^\circ$. It yields a *nitrosochloride*, m.p. 177°, a *nitrosobromide*, m.p. 144–145°, a *nitrosate*, m.p. 161° and a *nitrosite*, m.p. 116°. The three former give a *nitrolbenzylamine*, m.p. 126–128°, identical with one of the nitrolbenzylamines described by Kremers and Schreiner. By the action of sodium methoxide on the nitrosochloride an *α -methoxynitrosocaryophyllene*, $C_{16}H_{27}O_2N$, m.p. 116°, was obtained.

β -Caryophyllene, which is laevorotatory, is present mainly in the caryophyllene fraction, b.p. 129–130°/14 mm. ($\alpha_D - 8.5^\circ$ to -9.5°). It yields a *nitrosochloride*, m.p. 159°, $[\alpha]_D - 98.07^\circ$, and

* Wallach and Tuttle, *Annalen*, 1894, 279, 391.

† Schimmel's Report, 1904, 1, 80.

‡ *Annalen*, 1907, 356, 1; 1908, 359, 245; 1909, 369, 51; 1912, 388, 136; *J. pr. Chem.* 1911 [ii], 83, 483; 1914 [ii], 90, 324; 1926 [ii], 114, 63; 1927 [ii], 117, 273; 1928 [ii], 120, 133; 1929 [ii], 122, 261; compare Ramage and Simonsen, *J.C.S.* 1938, p. 1208.

§ *Helv. Chim. Acta*, 1931, 14, 410.

|| The question of the identity of α -caryophyllene and humulene is discussed on p. 112.

a blue *nitrosite*, m.p. 115° , $[\alpha]_D + 1661^{\circ}$, from both of which a *nitrolbenzylamine*, m.p. $172-173^{\circ}$, $[\alpha]_D + 226.26^{\circ}$ can be prepared. This is identical with Kremer's and Schreiner's second nitrolbenzylamine. If the blue nitrosite is exposed to light in benzene solution a substance, $C_{15}H_{19}O_6N_3$, m.p. 159.5° , results, whilst in alcoholic solution another substance, $C_{15}H_{22}O_4N_2$, m.p. 130.5° , can be obtained. The blue nitrosite was further characterised by the preparation of a blue *hydrochloride*, m.p. 140° , an orange yellow *bromonitrosite*, m.p. $104-105^{\circ}$, and a red *iodonitrosite*, m.p. 125° . β -Caryophyllene gives with hydrogen chloride an excellent yield of *caryophyllene dihydrochloride*, m.p. $69-70^{\circ}$. This dihydrochloride was first described by Schreiner and Kremers* and has been used since for the identification of caryophyllene. It does not appear to be established that it can be prepared from α -caryophyllene. Some of its more important reactions will be discussed later.

γ -Caryophyllene remains in the mother liquor after the preparation of β -caryophyllene nitrosite. It can be prepared also by heating the blue nitrosite with alcohol. When so obtained, it boils at $125-125.5^{\circ}/14.5$ mm., $d^{19}_{20} 0.8995$, $n^{19}_D 1.4966$, $[\alpha]_D - 26.17^{\circ}$. It can be characterised by the preparation of the *nitrosochloride*, which exists in two modifications, m.p. 122° , $[\alpha]_D + 14.71^{\circ}$, and m.p. 146° , $[\alpha]_D - 33.69^{\circ}$. They both yield the same *nitrolbenzylamine*, m.p. $172-173^{\circ}$, identical with that derived from β -caryophyllene nitrosochloride. γ -Caryophyllene gives caryophyllene dihydrochloride, when treated with hydrogen chloride. It is obvious from these reactions that β - and γ -caryophyllenes are closely related. This subject is discussed in greater detail on p. 63.

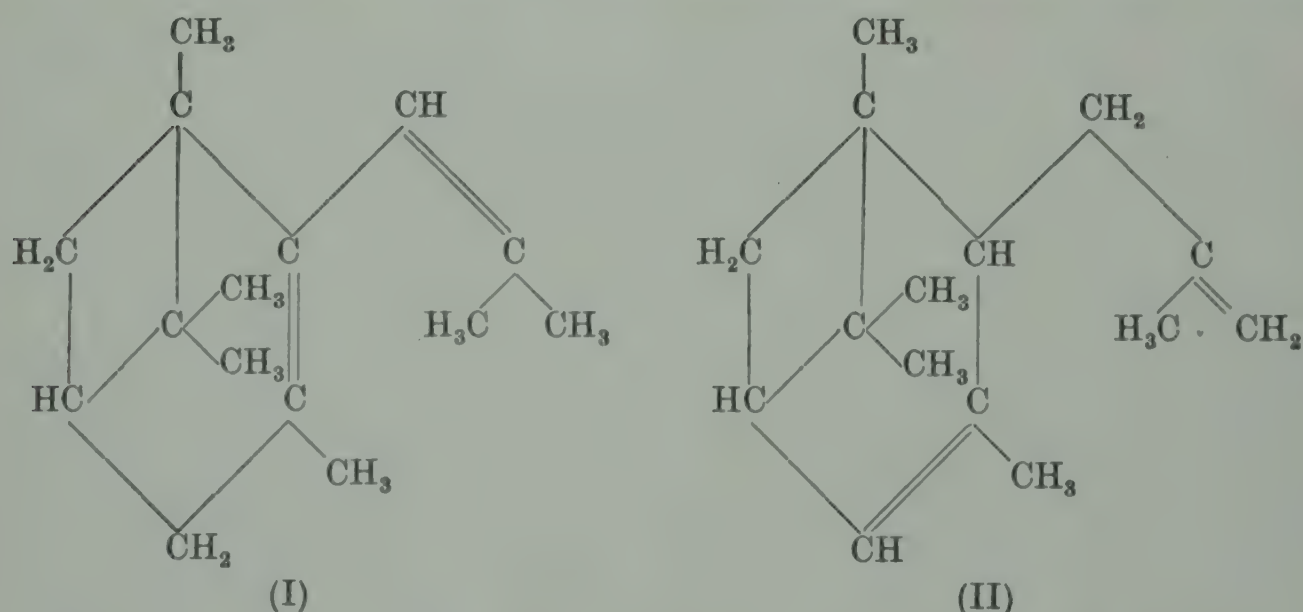
Since it is not possible to separate the caryophyllenes by fractional distillation, the majority of experiments on which their constitutions have been based have been carried out with the sesquiterpene mixture from oil of cloves. It can, however, be regarded as established, (i) that the β - and γ -caryophyllenes are dicyclic and contain two ethylenic linkages, since they yield a dihydrochloride, and (ii) that as part of the ring structure they must contain a *cyclobutane* ring with a *gem.*-dimethyl group,

* *Pharm. Arch.* 1899, 2, 296; 1902, 4, 164.

since both give norcaryophyllenic acid on oxidation (see p. 48).

By the oxidation of the hydrocarbons with potassium permanganate Haarmann,* and also Deussen, obtained a number of degradation products, but they threw little light on the structure of the parent hydrocarbons. Semmler and Mayer† were more successful in their study of the products formed on ozonolysis, and they suggested that the two principal hydrocarbons were represented by formulae (I) and (II), respectively.

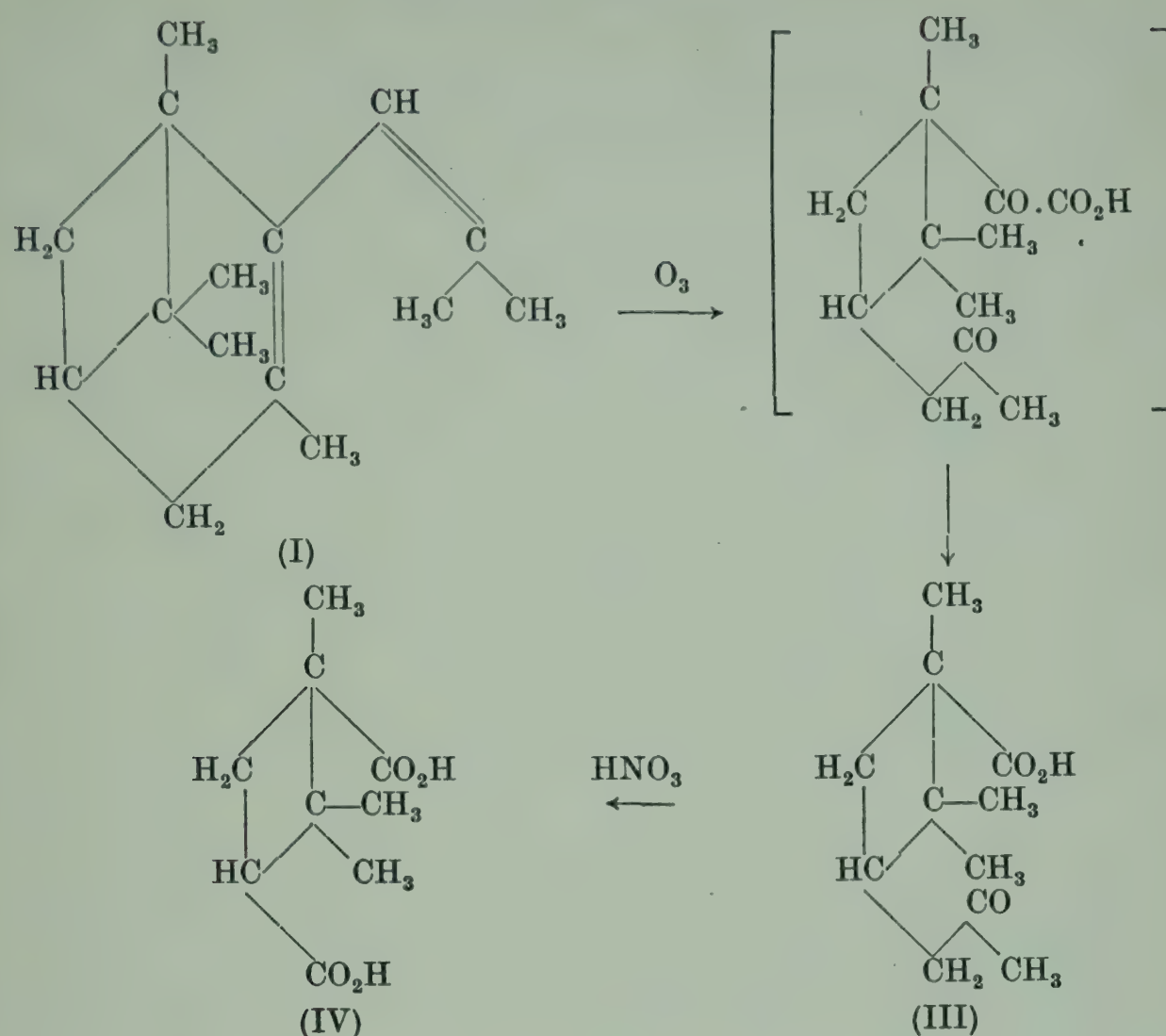
The evidence which was advanced for the presence of a hydrocarbon having the structure (I) was the following. One of the products of ozonolysis was a *ketonic acid*, $C_{11}H_{18}O_3$, b.p. 183–187°/11.4 mm., d^{20}_D 1.040, n^{20}_D 1.4677, $\alpha_D + 44^\circ$, *semicarbazone*, m.p. 183°, which gave on oxidation with nitric acid *as*-dimethylsuccinic acid and a dibasic acid, *caryophyllenic acid*, $C_9H_{14}O_4$, b.p. 215–218°/9 mm., *anhydride*, b.p. 152–158°/10 mm. (see below). This same mixture of acids was formed also, when the ketonic acid was oxidised with sodium hypobromite. The latter



reaction must proceed abnormally, since the oxidation of a ketonic acid, $C_{11}H_{18}O_3$, having the suggested structure (III), would be expected to yield a dibasic acid, $C_{10}H_{16}O_4$. From a consideration of its reactions Semmler and Mayer suggested that caryophyllenic acid was the *cyclobutane acid* (IV), the oxidation of (I) proceeding in accordance with the scheme on p. 43.

* *Ber.* 1909, **42**, 1062; 1910, **43**, 1505.

† *Ibid.* 1911, **44**, 3657.

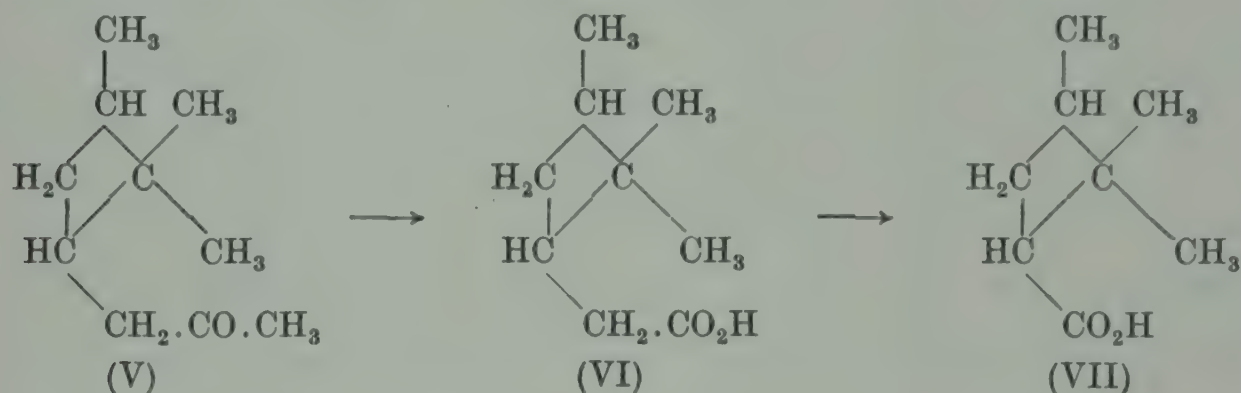


It will be observed that this represents the ketonic acid (III) as methylpinonic acid and caryophyllenic acid as a methylnorpinic acid. It is difficult to see why the former should not yield a methylpinic acid on oxidation with sodium hypobromite. Deussen and Hacker* attempted to confirm Semmler and Mayer's formula for caryophyllenic acid. They found that when caryophyllenic acid was fused with potassium hydroxide at 180° a mixture of acetic and isovaleric acids was obtained, but on bromination of the acid chloride a dibromo-acid resulted. It is obvious that the two former acids could be formed by the fission of the *cyclobutane* ring, but it is difficult to account for the isolation of a dibromocaryophyllenic acid on the basis of Semmler and Mayer's structure, although Deussen and Hacker did not on this account reject it.

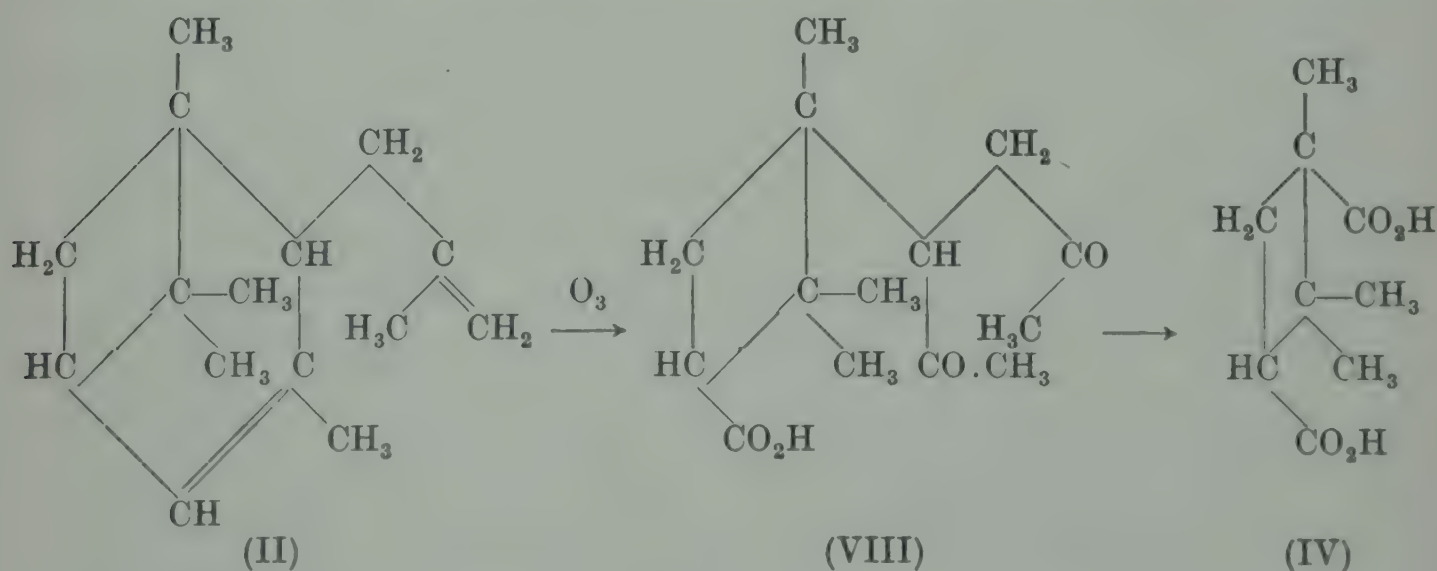
From amongst the neutral products formed in the oxidation, a *ketone*, $C_{10}H_{18}O$, b.p. 73–76°/11.5 mm., d^{20}_D 0.8823, n^{20}_D 1.4387, α_D -7° , *semicarbazone*, m.p. 176°, was isolated. To this ketone

* *J. pr. Chem.* 1929 [ii], 122, 261.

Semmler and Mayer gave the structure (V), since, on oxidation with sodium hypobromite, it gave an *acid* (VI), $C_9H_{16}O_2$, b.p. $131-133^\circ/12.5$ mm., *amide*, m.p. 114° , whilst with nitric acid the *acid* (VII), $C_8H_{14}O_2$, b.p. $119-122^\circ/12$ mm., *amide*, m.p. $115-116^\circ$, was obtained. The formulae assigned to these substances are, however, completely devoid of experimental foundation, the more so since the formula assigned by Semmler and Mayer to the parent hydrocarbon is incorrect.



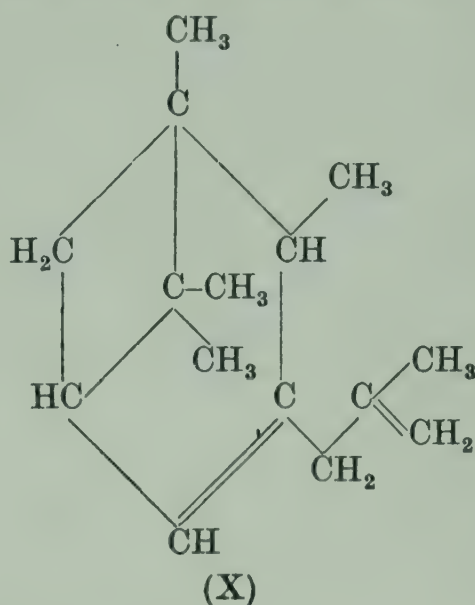
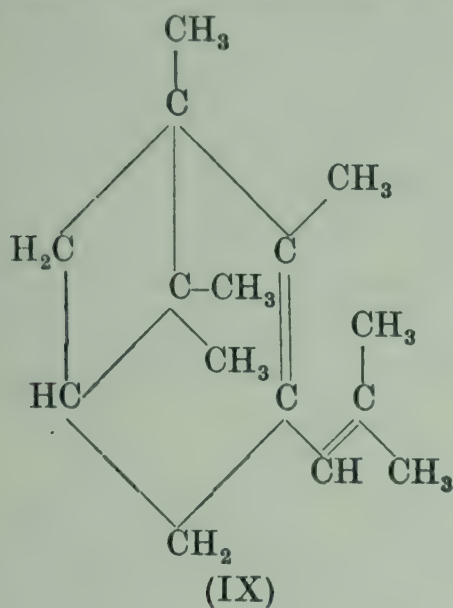
For the occurrence of a second hydrocarbon (II) the following evidence was advanced. The second main product of ozonolysis was a *diketonic acid*, $C_{14}H_{22}O_4$, b.p. $229-232^\circ/11.5$ mm., d^{20}_D 1.0830, n^{20}_D 1.4804, $\alpha_D + 41^\circ$, *semicarbazone*, m.p. about 120° . This acid gave, on oxidation with nitric acid, caryophyllenic and *as*-dimethylsuccinic acids. The diketonic acid was assumed to have formula (VIII) and considered to be a derivative of (II).



In 1924 Busse* suggested (IX) and (X) as alternative formulae for caryophyllene. He considered these to be more in accord with the general assumption that the sesquiterpenes are built up

* *Abt. d. Wissensch. Chem. Pharm. Inst. Moscow*, 1924, 10, 77.

from three isoprene nuclei. He did not, however, put forward any new experimental evidence in support of his formulae.



If Semmler and Mayer's formula (I) and Busse's formula (IX) be inspected, it will be observed that they contain a system of conjugated ethylenic linkages. It would be anticipated, therefore, that a caryophyllene represented by these formulae might be reduced by sodium in alcoholic solution and would possess a characteristic absorption spectrum in the ultra-violet. The caryophyllenes cannot be reduced by sodium in alcoholic solution* and the absorption spectrum shows that at the most only a few per cent of conjugated isomers can be present.† It follows therefore that these formulae must be incorrect, and since Busse's modification necessitates such a system in one of the isomerides, both (IX) and (X) must be rejected.

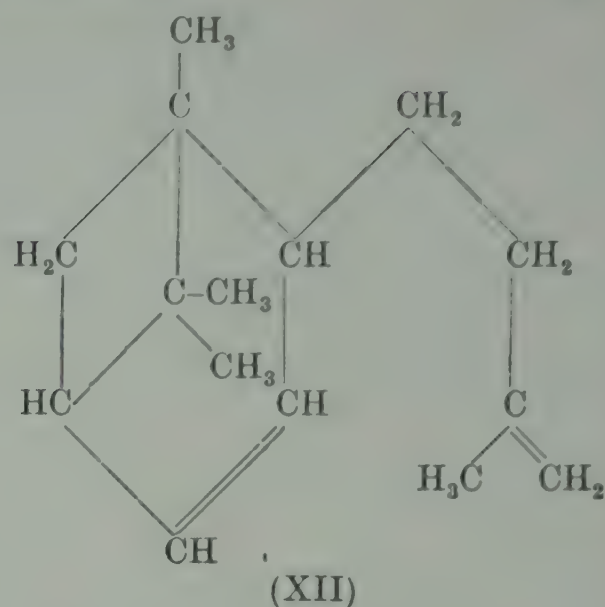
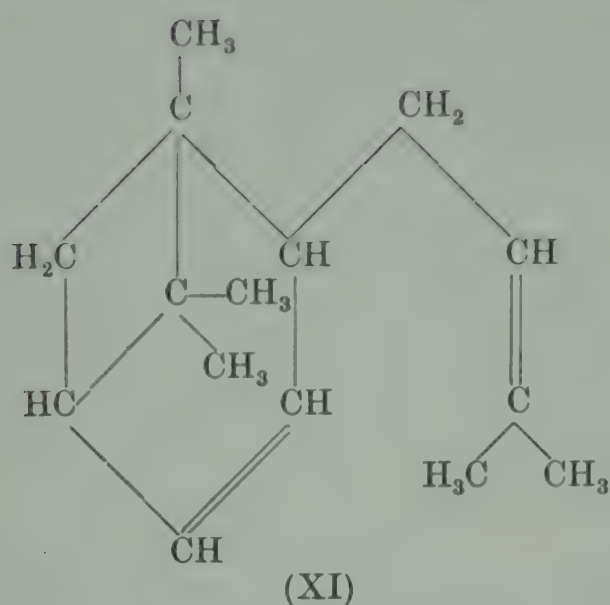
Deussen suggested that Semmler and Mayer's formulae (I) and (II) should be replaced by (XI) and (XII), which he considers to accord best with the reactions of β - and γ -caryophyllenes. He endeavoured to provide evidence in support of these formulae and more especially to determine which should be assigned to β -caryophyllene and which to γ -caryophyllene.

Deussen drew attention to the fact that the two ethylenic linkages in caryophyllene could not be similarly situated. Although on catalytic hydrogenation in the presence of platinum *tetrahydrocaryophyllene*, $C_{15}H_{28}$, b.p. 122–123°/12 mm., d^{20}_D 0.8712, n_D 1.4700, $\alpha_D + 3^\circ$, was formed,‡ if palladium was used as the

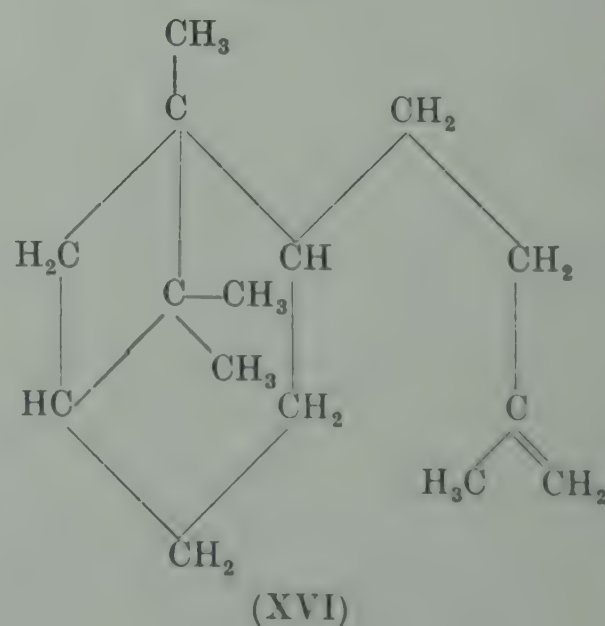
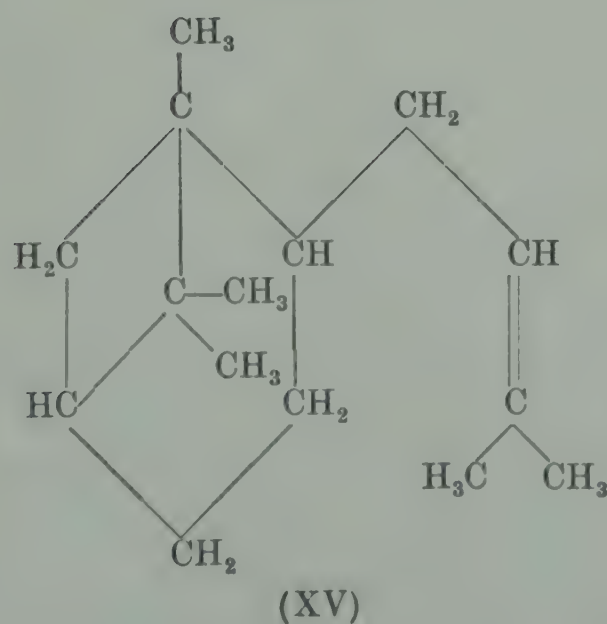
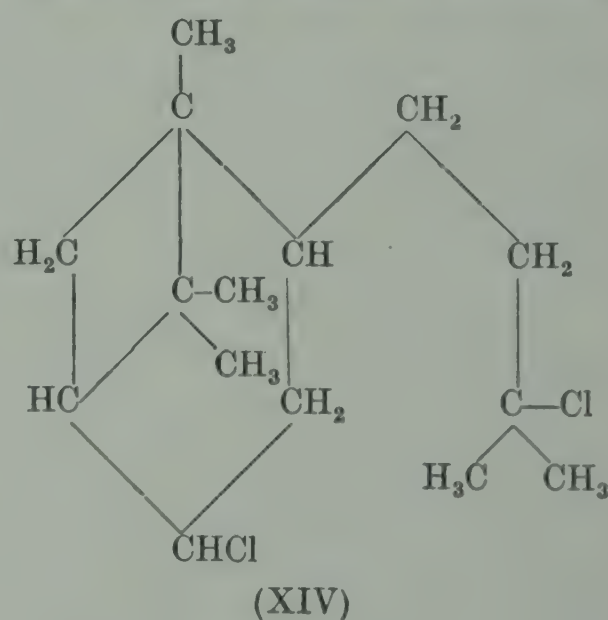
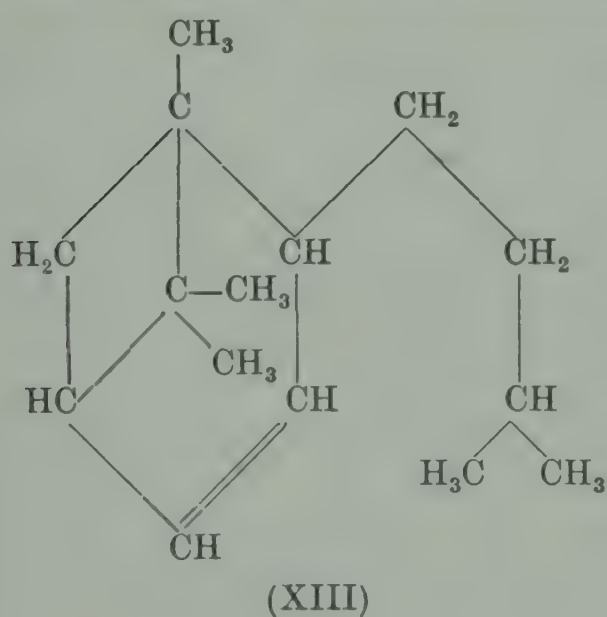
* Naves and Perrottet, *Helv. Chim. Acta*, 1941, **24**, 790.

† *Idem, ibid.*; Goodway and West, *J.C.S.* 1939, p. 1853.

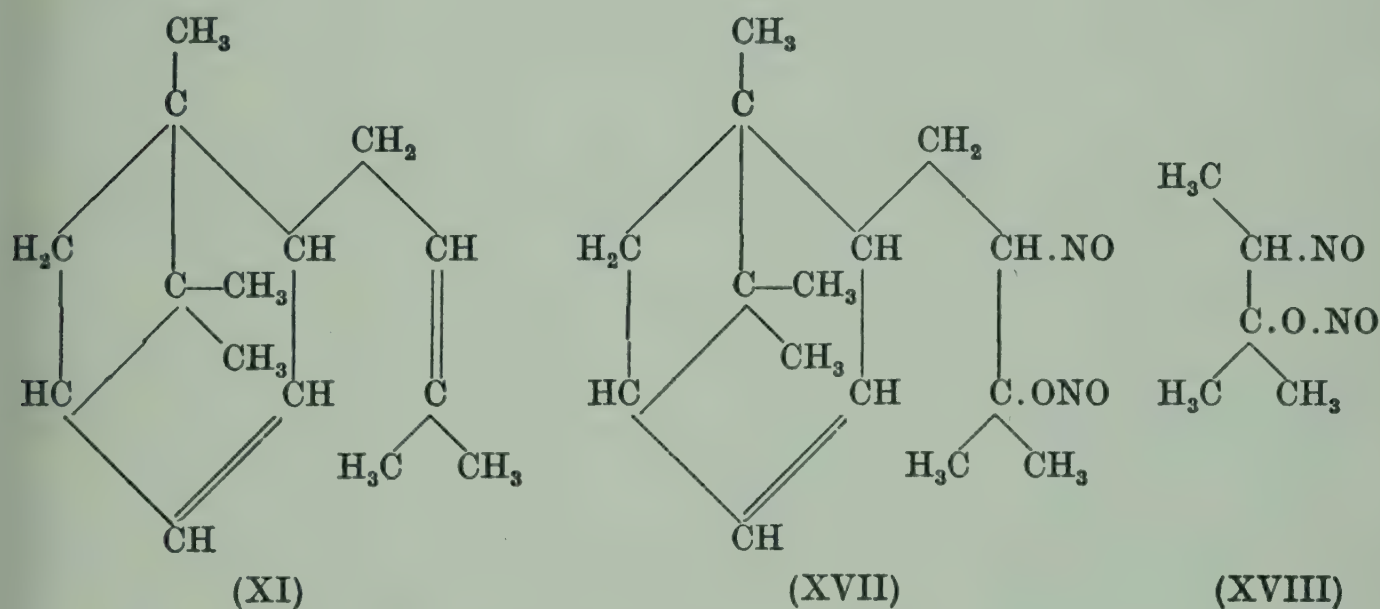
‡ Semmler and Mayer, *Ber.* 1912, **45**, 1393; compare Naves and Perrottet, *loc. cit.*



catalyst, then a *dihydrocaryophyllene*, b.p. 129–130°/14 mm., $\alpha_D - 32.7^\circ$ was obtained. This hydrocarbon, which still contained an ethylenic linkage, since it reacted with hydrogen bromide, was extremely resistant to potassium permanganate and it was not attacked by mercuric acetate. Adopting Deussen's formulae,



this hydrocarbon is most probably represented by (XIII). A second *dihydrocaryophyllene*, b.p. $131^{\circ}/11$ mm., $d_4^{15^{\circ}} 0.8965$, $n_D^{18^{\circ}} 1.496$, $\alpha_D - 4.97^{\circ}$, has been prepared by the action of methyl magnesium iodide on caryophyllene dihydrochloride (XIV). There can be no doubt that this must have an exocyclic ethylenic linkage, since it is immediately attacked by potassium permanganate and it may be represented, on the basis of Deussen's formulae (XI) and (XII), by (XV) or (XVI), and it is not improbably a mixture. Deussen considered that formula (XI) should be assigned to β -caryophyllene, since its nitrosite (XVII) resembled very closely in its properties *trimethylethylene nitrosite* (XVIII). γ -Caryophyllene would then be represented by (XII) (see p. 46).



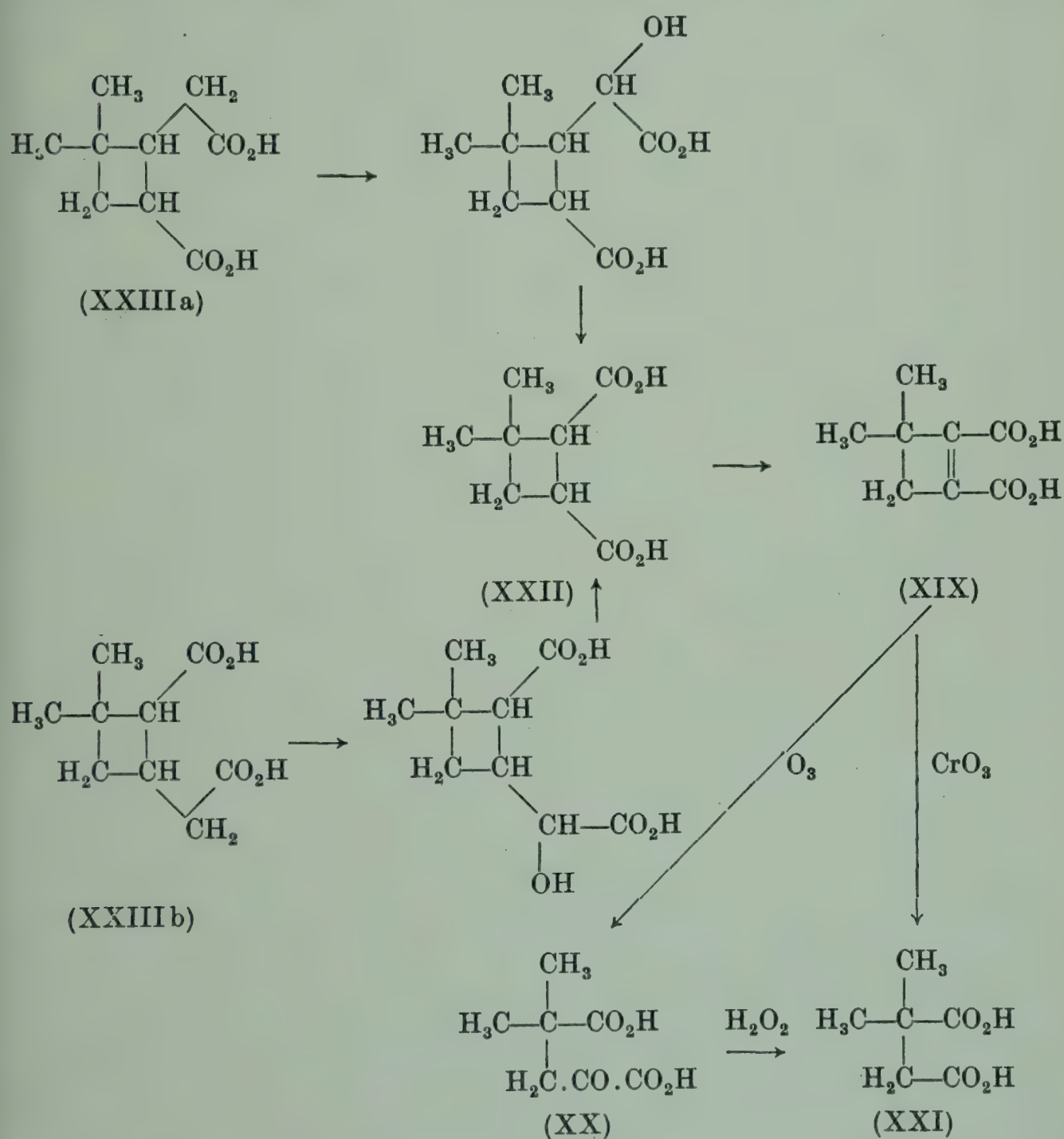
It will be recalled that Semmler and Mayer's experiments on the ozonolysis of caryophyllene were carried out with the sesquiterpene mixture from oil of cloves. Deussen and Hacker* have investigated the action of ozone on γ -caryophyllene. An *ozonide*, $C_{15}H_{24}O_6$, was obtained, which gave on decomposition formaldehyde and formic acid in accordance with anticipation. Unfortunately they were not able to characterise the other products of the reaction, although caryophyllenic acid was obtained on further oxidation with nitric acid. One primary product of the ozonolysis was succinic acid; the formation of this substance was unexpected and might have resulted from the oxidation of the long side chain.

* *J. pr. Chem.* 1927 [ii], 117, 273; 1929 [ii], 122, 261.

On the basis of Deussen's formulae for β - and γ -caryophyllenes, it is very difficult to account for the degradation products obtained by Semmler and Mayer (p. 42) by the ozonolysis of the mixed caryophyllene hydrocarbons, and, indeed, all these earlier formulae are now only of historic interest, since they have been completely disproved by the more recent investigations on caryophyllenic acid. As mentioned on p. 43 Semmler and Mayer suggested that this acid, which was not obtained crystalline, was a methylnorpinic acid and this formula was generally accepted, although it was unsupported by any direct experimental evidence. However, Ruzicka, Bardhan and Wind* demonstrated the inhomogeneity of the acid and, shortly afterwards, Evans, Ramage and Simonsen† were able to show that the liquid "caryophyllenic acid" actually consisted of two homologous acids, d-trans-caryophyllenic acid, $C_9H_{14}O_4$, m.p. 80–81°, $[\alpha]_{5461} + 13.56^\circ$, $[\alpha]_D + 28.2^\circ$ (in benzene), dimethyl ester, b.p. 119–119.5°/12 mm., $d_4^{22^\circ} 1.041$, $n_D^{22^\circ} 1.4439$, $\alpha_D + 47.9^\circ$, $[\alpha]_D + 44.5^\circ$ (in methanol), dianilide, m.p. 282°, $[\alpha]_D^{52^\circ} + 19^\circ$ (in pyridine),‡ and d-trans-norcaryophyllenic acid, $C_8H_{12}O_4$, m.p. 125–127°, $[\alpha]_{5461} + 137^\circ$ (in chloroform), $[\alpha]_D + 118^\circ$ (in chloroform), $[\alpha]_D^{15^\circ} + 91.8^\circ$ (in benzene), dimethyl ester, b.p. 107°/12 mm., $d_4^{22^\circ} 1.0506$, $n_D^{22^\circ} 1.4393$, $\alpha_D + 47.9^\circ$, $[\alpha]_D^{20^\circ} + 59.5^\circ$ (in methanol), dianilide, m.p. 178–179°, $[\alpha]_D^{15^\circ} + 170^\circ$ (in chloroform), $[\alpha]_D^{15^\circ} + 81.3^\circ$ (in pyridine). When the latter acid was converted to the di-acid chloride and brominated, either a monobromo-derivative (not isolated in a state of purity) or a dibromo-derivative, $C_8H_{10}O_4Br_2$, m.p. 202° was formed depending on the reaction conditions. The monobromo-derivative, on treatment with alcoholic potassium hydroxide, furnished dehydronorcaryophyllenic acid, $C_8H_{10}O_4$, m.p. 194°, which on oxidation with chromic acid afforded as-dimethylsuccinic acid. Proof that dehydronorcaryophyllenic acid must be represented by (XIX) resulted from a study of its oxidation with ozone. The primary product was α' -keto- $\alpha:\alpha$ -dimethylglutaric acid, $C_7H_{10}O_5$ (XX), phenylsemicarbazone, decomp. 165°, p-nitrophenylhydrazone, decomp. 192°, which on further oxidation with hydrogen peroxide in alkaline solution gave as-

* *Helv. Chim. Acta*, 1931, 14, 423.† *J.C.S.* 1934, p. 1806.‡ See Ruzicka and Zimmermann, *Helv. Chim. Acta*, 1935 18, 219; Ruzicka, Plattner and Werner, *ibid.* 1943, 26, 966.

dimethylsuccinic acid (XXI). A rigid experimental proof was thus provided that *d-trans*-norcaryophyllenic acid must be (XXII) as had been suggested independently by Ruzicka and Zimmermann,* and by Ramage and Simonsen.† This structure was confirmed by Rydon's synthesis‡ of *dl-trans*-norcaryophyllenic acid, m.p. 148–149°, which he resolved into its optical enantiomorphs, the *d*-form being identical with the acid derived from the caryophyllenes. He prepared also *dl-cis*-norcaryophyllenic acid, m.p. 149–150°, *d*- and *l*-forms, m.p. 105°, $[\alpha]_D + 5.9^\circ$ and -5.9° respectively (in chloroform), *anhydride*, m.p. 40–41°.

* *Loc. cit.*† *Ibid.* 1936, p. 593; 1937, p. 1340.† *J.C.S.* 1935, p. 532.

Since *d-trans*-caryophyllenic acid could be degraded to *d-trans*-norcaryophyllenic acid by the method used by Baeyer for the preparation of norpinic acid from pinic acid (see Vol. II, p. 115), it followed that it must be represented by either (XXIIIa) or (XXIIIb). In agreement with either of these formulae *d-trans*-caryophyllenic acid gave a *dibromo-acid*, $C_9H_{12}O_4Br_2$, m.p. 198° , on bromination of its acid chloride.*

It is still not possible to decide for certain which of the two structures (XXIIIa) and (XXIIIb) represents *d-trans*-caryophyllenic acid.† When the dimethylester was treated with phenyl magnesium bromide the *tetraphenyl glycol* (XXIVa) or (XXIVb), $C_{33}H_{34}O_2$, m.p. $198-199^\circ$, was formed, whilst with methyl magnesium iodide the corresponding *tetramethyl glycol* (XXVa) or (XXVb), $C_{13}H_{26}O_2$, m.p. $99-100^\circ$ resulted. The tetraphenyl glycol, on oxidation with chromic acid, formed benzophenone and *as*-dimethylsuccinic acid. With formic or acetic acids one molecule of water was lost to give a *monohydroxy* compound, (XXVIa) or (XXVIb), b.p. $240^\circ/3\text{ mm.}$, which gave benzophenone and unidentified products on ozonolysis. A similar *tetraphenyl glycol*, $C_{32}H_{32}O_2$ (XXVII), was formed from *d-trans*-norcaryophyllenic acid and this also gave benzophenone and *as*-dimethylsuccinic acid on oxidation with chromic acid.

The tetramethyl glycol from *d-trans*-caryophyllenic acid behaved, however, in an abnormal and unexpected fashion on chromic acid oxidation yielding $\alpha:\alpha:\alpha':\alpha'$ -*tetramethylglutaric acid* (XXVIII), m.p. $192-193^\circ$, *anhydride*, m.p. 89° .‡ This can be most readily explained if it is assumed that a retropinacolinic rearrangement occurs, either during the preparation of the tetramethyl glycol, or during its oxidation, more probably the former. If this explanation of the formation of the tetramethylglutaric acid be correct, then caryophyllenic acid must be represented by (XXIIIa) and not (XXIIIb) as is shown in the scheme on p. 52.§ Definite proof must, however, await the synthesis of this acid. If the structure (XXIIIa) be now accepted as representing *d-trans*-caryophyllenic acid, then the formula (XXIX), proposed

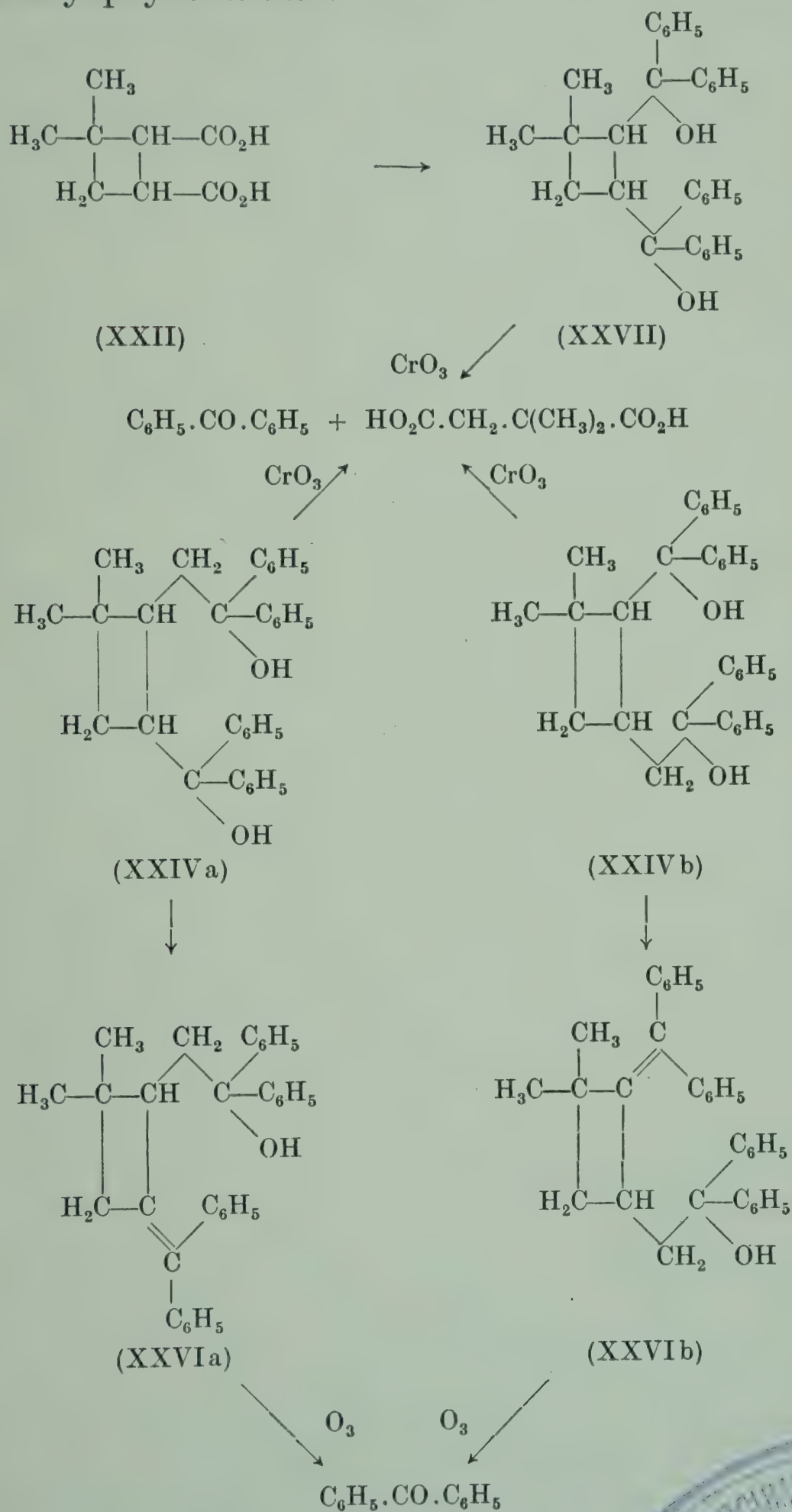
* Ramage and Simonsen, *loc. cit.*

† The very recent synthesis by Dawson and Ramage (*J.C.S.* 1950, p. 3523) of the acid represented by (XXIIIb) has shown *d-trans*-caryophyllenic acid to be (XXIIIa).

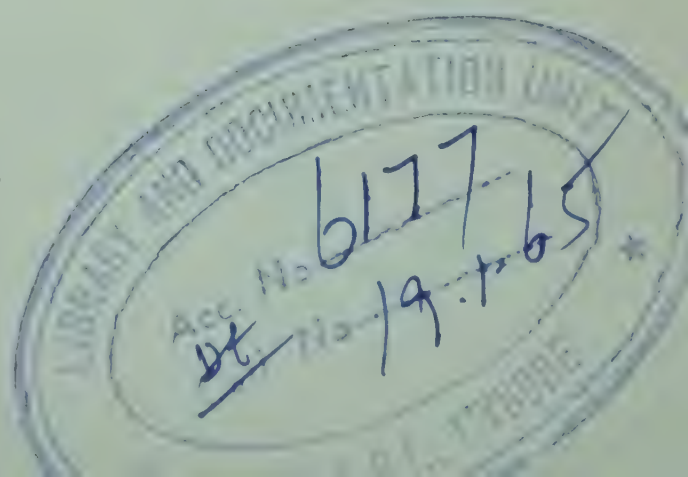
‡ Ruzicka, Bardhan and Wind, *Helv. Chim. Acta*, 1931, **14**, 423.

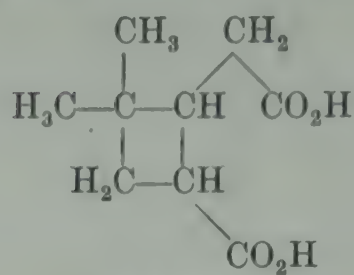
§ Barton, *J. Org. Chem.* 1950, **15**, 457.

by Ramage and Simonsen,* for β -caryophyllene becomes untenable, since it would lead to the alternative (XXIIIb) for *d-trans*-caryophyllenic acid.

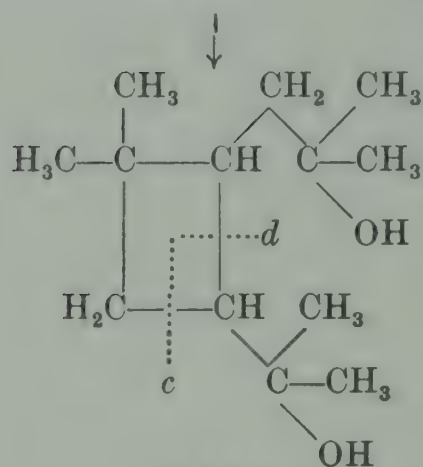


* J.C.S. 1935, p. 1581.

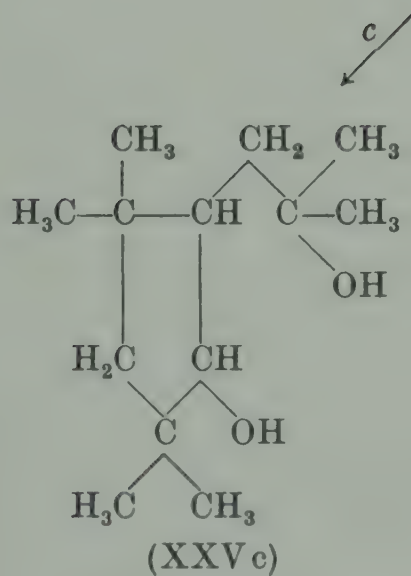




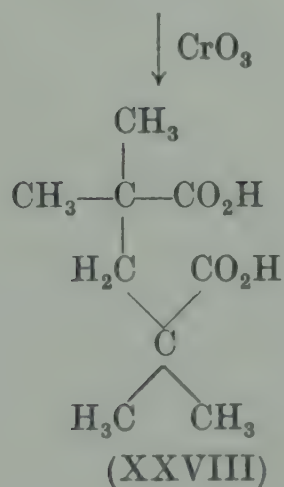
(XXIII a)



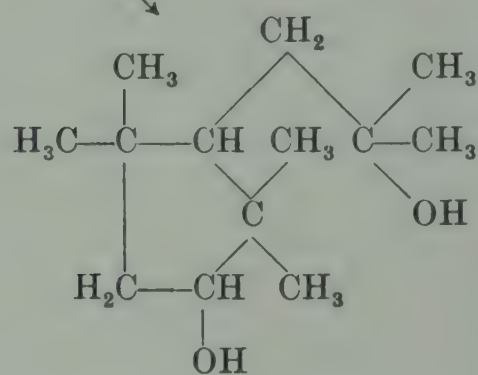
(XXV a)



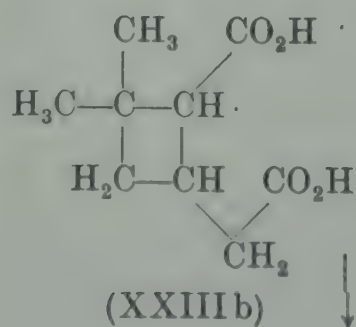
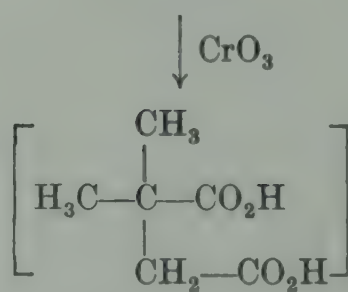
(XXV c)



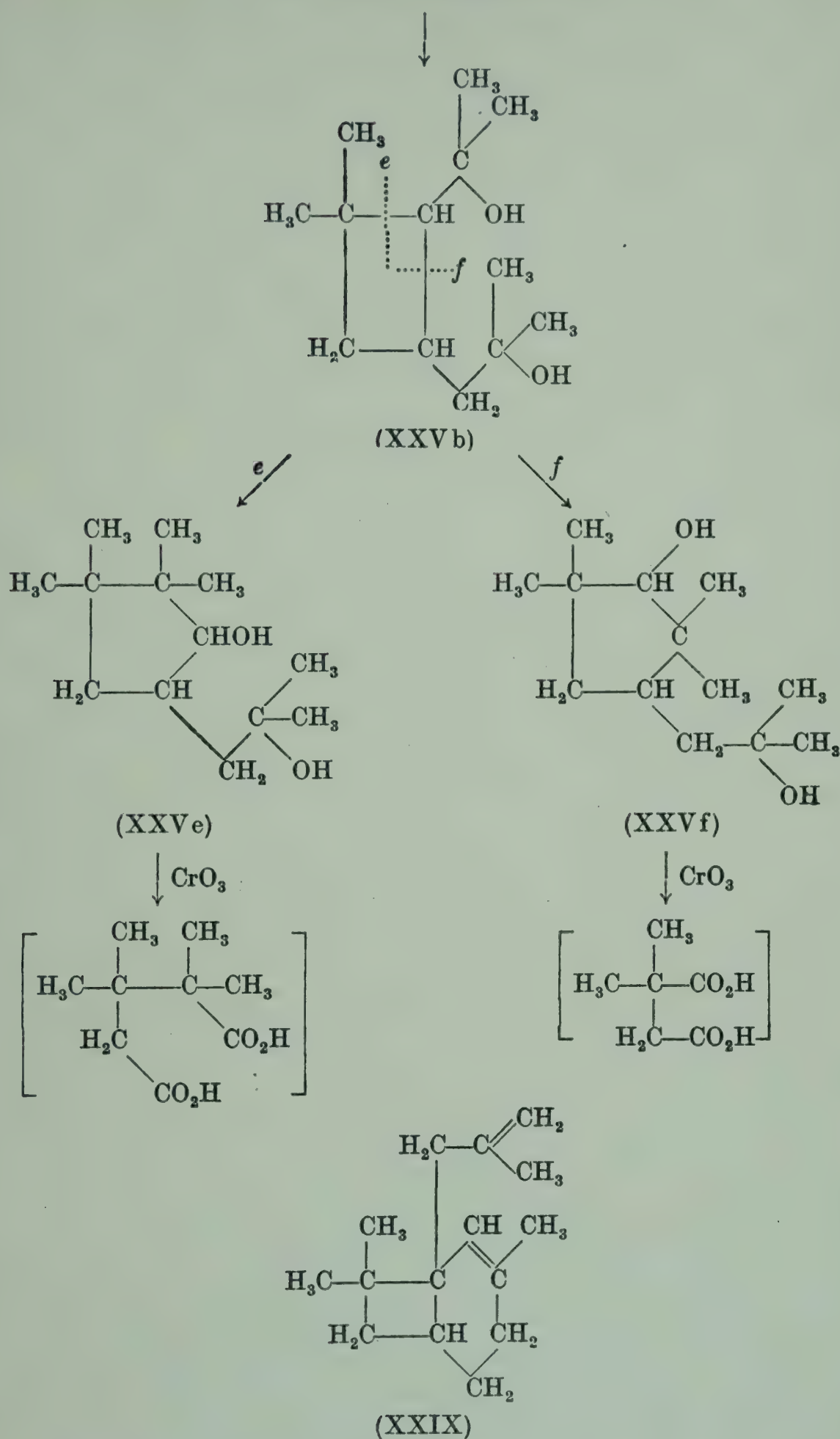
(XXVIII)



(XXV d)



(XXIII b)



Since the caryophyllenic acid obtained from the caryophyllenes could be degraded to *d-trans*-norcaryophyllenic acid (p. 48), it had been concluded that the former acid had the con-

figuration *d-trans*-, as has been assumed in the above discussion. This view has been confirmed by Ramage and Simonsen,* who found that *d-trans*-caryophyllenic acid, when heated with acetic anhydride at 220°, was converted to *cis*-caryophyllenic acid anhydride, b.p. 157–158°/12 mm., which yielded, on hydration, *cis*-caryophyllenic acid, m.p. 74–75°, $[\alpha]_D^{21} - 45.3^\circ$ (in benzene), $[\alpha]_{5461} - 7.4^\circ$ (in chloroform), *dimethyl ester*, b.p. 85°/0.5 mm., $n_D^{20} 1.4465$, $[\alpha]_D^{20} - 36.3^\circ$ (in benzene), *dianilide*, m.p. 198–199°, $[\alpha]_D^{20} - 161^\circ$ (in chloroform), *di-p-phenacyl ester*, m.p. 121–122°.

Ruzicka and Wind† have re-examined the oxidation products obtained on ozonolysis of the caryophyllenes, which were described originally by Semmler and Mayer (p. 42). On the basis of the formula (XXX) suggested later by Ruzicka‡ for β -caryophyllene new structures have been assigned to them. The diketoid acid, $C_{14}H_{22}O_4$, *methyl ester*, b.p. 151–152°/0.5 mm., $d_4^{19} 1.0453$, $n_D^{19} 1.4569$, is now represented by (XXXI) and the monoketo-acid, $C_{11}H_{18}O_3$, *methyl ester*, b.p. 127–130°/12 mm., $d_4^{20} 0.9981$, $n_D^{20} 1.4520$, $\alpha_D + 44.2^\circ$, by (XXXII). Although the diketoid acid could be hydrolysed by cold alcoholic sodium hydroxide, it underwent ring closure on digestion with alcoholic sodium ethoxide yielding an unsaturated keto-acid, $C_{14}H_{20}O_3$ (XXXIII), *methyl ester*, b.p. 143–146°/0.5 mm., $d_4^{18} 1.058$, $n_D^{18} 1.497$. By the oxidation of this acid with sodium hypobromite a dicarboxylic acid, $C_{13}H_{18}O_4$ (XXXIV), m.p. 148–149°, *dimethyl ester*, b.p. 128–129°/0.3 mm., $d_4^{17} 1.0775$, $n_D^{17} 1.4894$, yielding on ozonolysis a keto-dicarboxylic acid, $C_{12}H_{18}O_5$ (XXXV), *dimethyl ester*, b.p. 135–136°/0.3 mm., $d_4^{18} 1.0856$, $n_D^{18} 1.4625$, was obtained, which on catalytic hydrogenation gave the saturated dicarboxylic acid, $C_{13}H_{20}O_4$ (XXXVI), m.p. 149°.

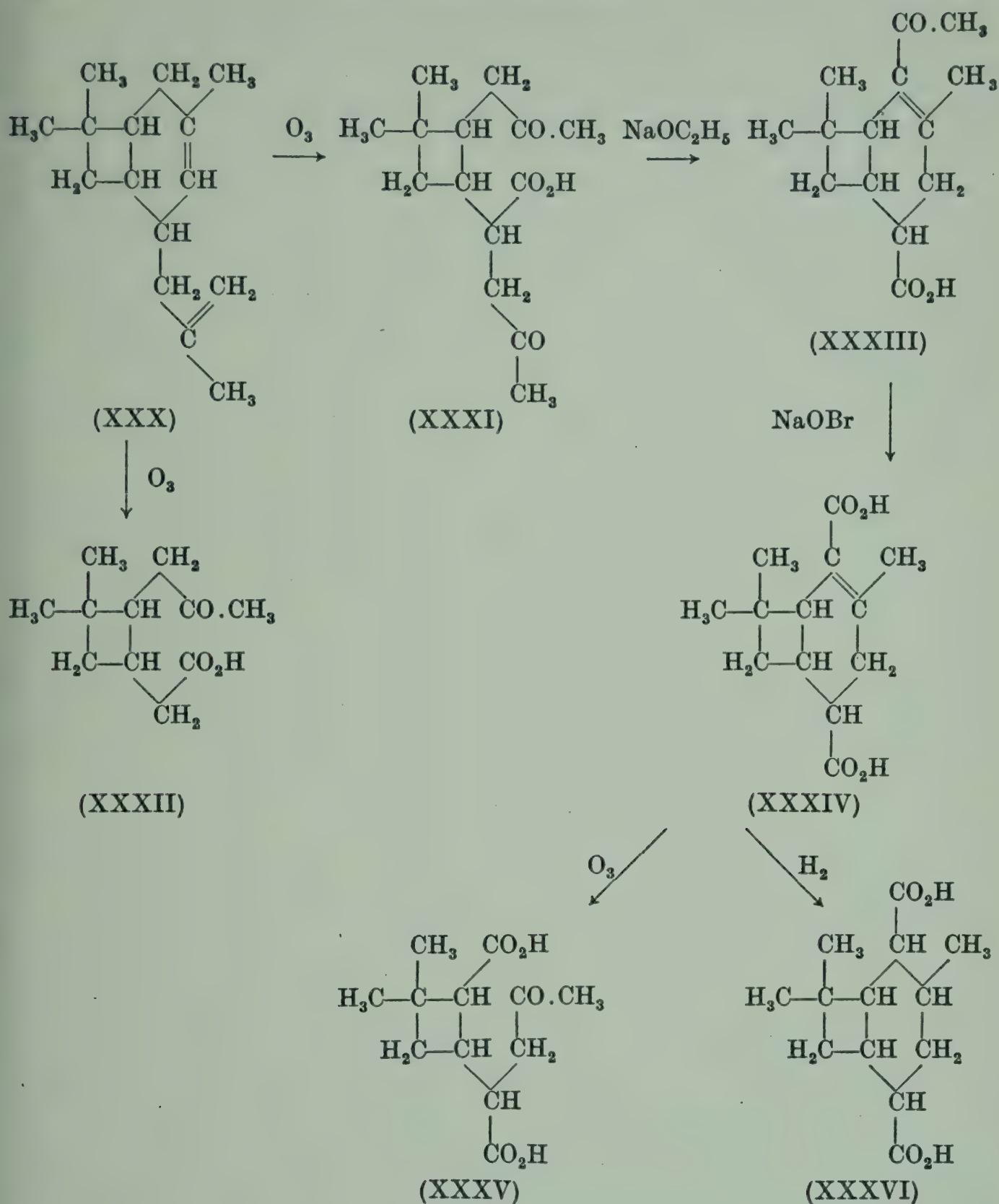
The oxidation of the monoketo-acid, $C_{11}H_{18}O_3$ (XXXII), has been investigated by Ruzicka and Wind and also by Ramage and Simonsen,§ who showed that it was degraded smoothly by sodium hypobromite to *d-trans*-homocaryophyllenic acid, $C_{10}H_{16}O_4$ (probably (XXXVII)), $[\alpha]_D + 105^\circ$ (in benzene), *dimethyl ester*, b.p. 90°/0.5 mm., $d_4^{21} 1.048$, $n_D^{20} 1.4514$, *dianilide*, m.p. 183–184°, $[\alpha]_D^{22} - 71.4^\circ$ (in chloroform). The assignment of the *trans*-

* J.C.S. 1936, p. 741; compare Ruzicka, Plattner and Werner, *loc. cit.*

† *Helv. Chim. Acta*, 1931, 14, 422.

‡ *Chem. and Ind.* 1935, 54, 509.

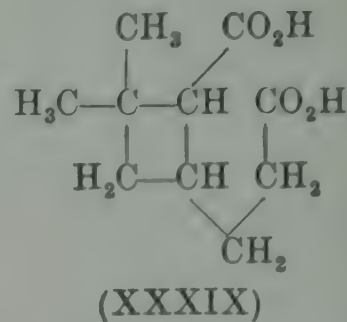
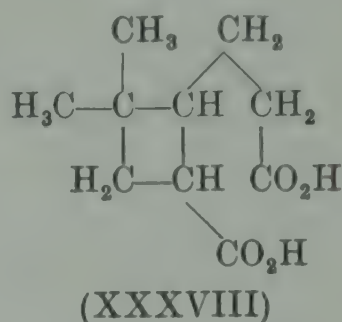
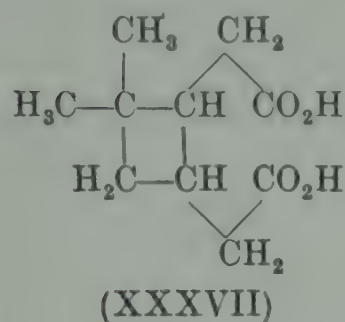
§ J.C.S. 1937, p. 73.



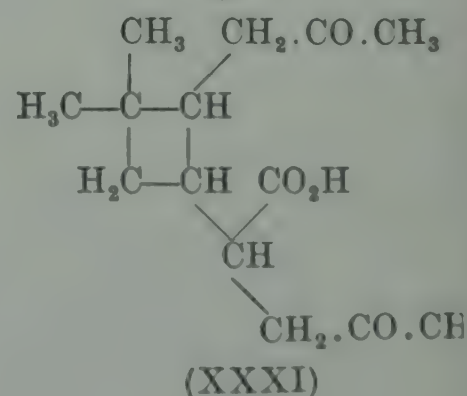
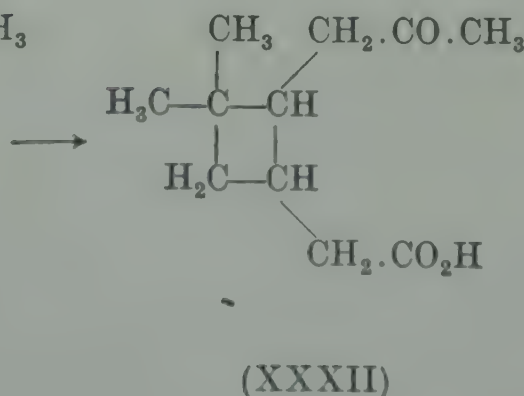
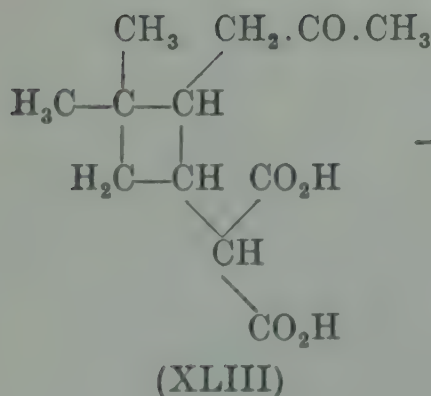
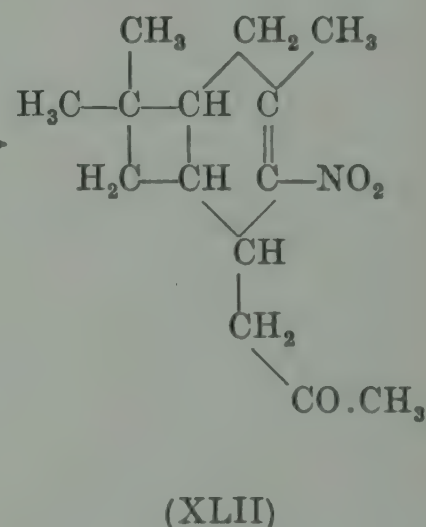
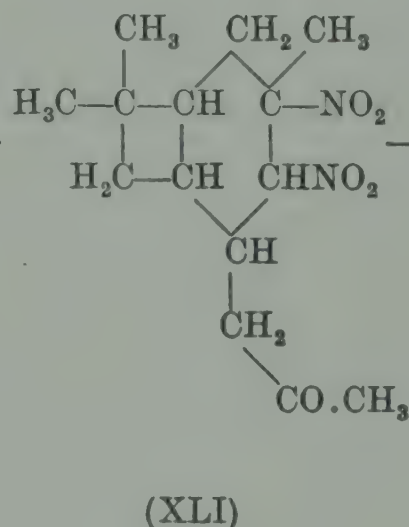
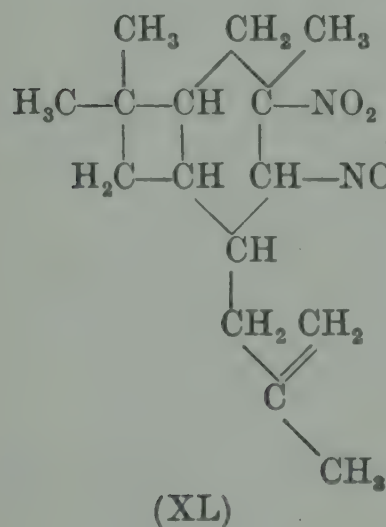
configuration to this acid is by analogy, since the maleic anhydride adduct of caryophyllene (see p. 68) gives on ozonolysis followed by oxidation with potassium permanganate a mixture of *d-trans*-norcaryophyllenic, *d-trans*-caryophyllenic and *d-trans*-homocaryophyllenic acids.

A partial synthesis of homocaryophyllenic acid was attempted by Ramage and Simonsen (*loc. cit.*) and although the interpretation of their results was made difficult by racemisation, the

conclusion was drawn that (XXXVII) rather than (XXXVIII) or (XXXIX) represented the acid.



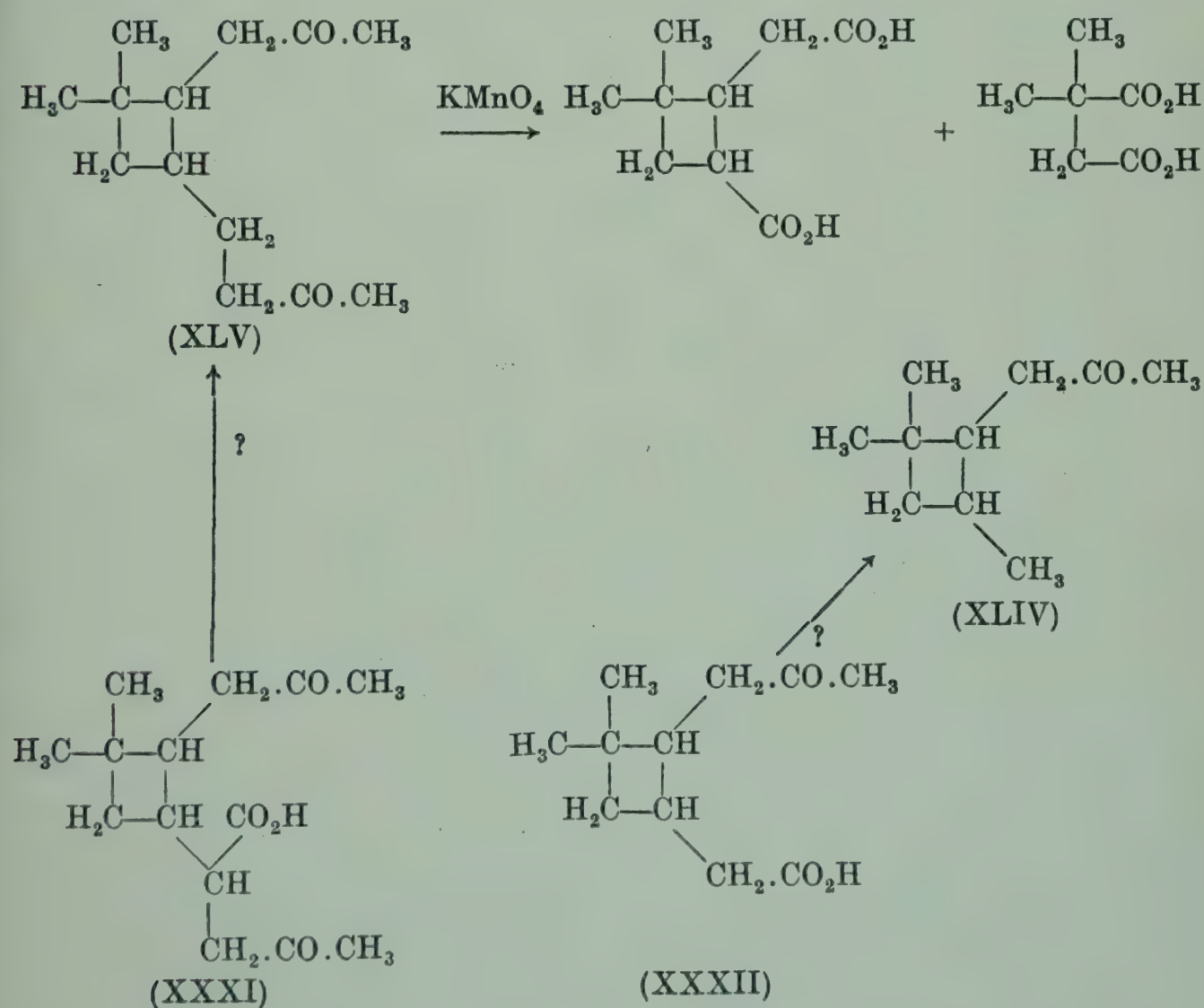
All the experiments discussed above are open to the criticism that there is no evidence for the homogeneity of the liquid hydrocarbons used and it is in fact known that in the majority of cases a mixture was employed. Ramage and Simonsen* studied therefore the ozonolysis of the crystalline β -caryophyllene nitrosite, m.p. 115° , which for convenience may be represented by (XL). In ethyl acetate-carbon tetrachloride solution formaldehyde and a colourless *ketone*, $\text{C}_{14}\text{H}_{22}\text{O}_5\text{N}_2$ (XLI), m.p. 161.5° , $[\alpha]_{5461} -33.6^\circ$, *phenylsemicarbazone*, decomp. 224° , *2:4-dinitrophenylhydrazone*, decomp. 225° , were obtained. Using acetic acid as



* J.C.S. 1935, p. 1581.

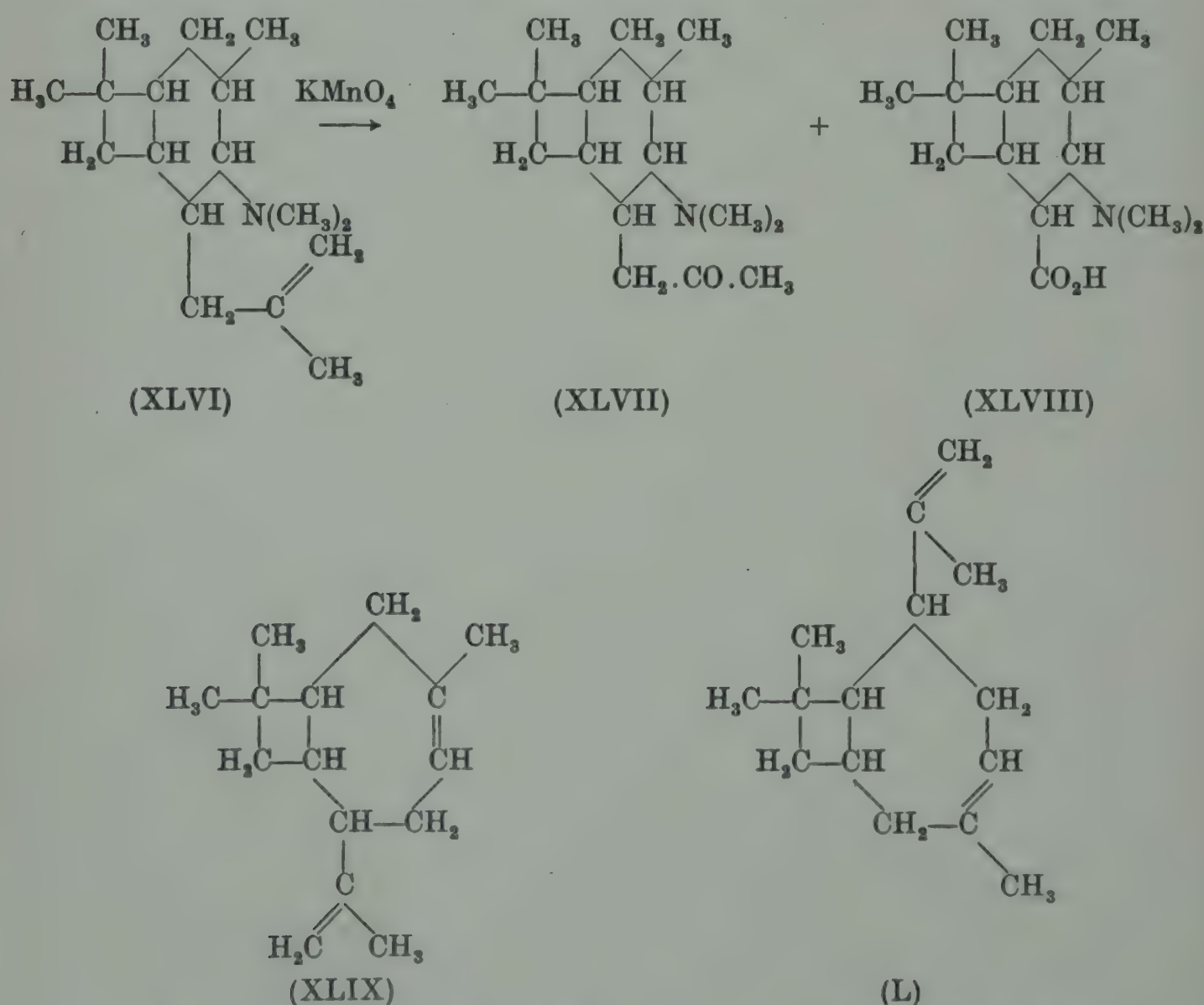
the solvent the ketone (XLI) formed was blue in colour, but was easily converted to the colourless form on heating in the same solvent. The colourless ketone (XLI) readily lost nitrous acid on warming with pyridine to yield an unsaturated *mononitroketone*, $C_{14}H_{21}O_3N$ (XLII), m.p. 69° , $[\alpha]_{5461} -114^\circ$ (in chloroform), *semicarbazone*, m.p. $186-187^\circ$, which on oxidation with ozone formed the diketonic acid (XXXI), *bis-2:4-dinitrophenylhydrazone*, decomp. $108-110^\circ$. A by-product in the ozonolysis of β -caryophyllene nitrosite was a nitrogen containing acidic substance which, after heating with pyridine and oxidation of the product with potassium permanganate, afforded a *malonic acid* (probably (XLIII)), which lost carbon dioxide on heating at 180° with formation of the ketonic acid (XXXII). These experiments are of importance because they definitely show that both (XXXI) and (XXXII) are derived, at least in part, from pure β -caryophyllene.

In addition to the various acids, which have already been discussed, and the monoketone, $C_{10}H_{18}O$ (see p. 43) now reformulated as (XLIV), two further neutral products have been ob-



tained by ozonolysis of the caryophyllenes.* One is a *substance*, $C_{14}H_{22}O_2$, m.p. 113° , which has not been thoroughly investigated, whilst the second is a *diketone*, $C_{13}H_{22}O_2$, b.p. $136^\circ/12$ mm., *disemicarbazone*, m.p. 219° , for which the formula (XLV) was suggested, since it gave on oxidation with potassium permanganate *d-trans*-caryophyllenic acid and *as*-dimethylsuccinic acid.

Further evidence in support of the suggested *isobutenyl* side chain in β -caryophyllene has been obtained by Ramage and Simonsen.† They showed that *dimethylaminodihydro- β -caryophyllene*, $C_{17}H_{31}N$ (XLVI), b.p. $154^\circ/12$ mm., prepared from aminodihydro- β -caryophyllene (p. 68), was oxidised by potassium permanganate in acid solution giving a *ketone*, $C_{16}H_{29}ON$ (XLVII), b.p. $170-175^\circ/12$ mm., and an *acid*, $C_{14}H_{25}O_2N$ (XLVIII), *methyl ester*, b.p. $175-180^\circ/12$ mm. The formation of this acid proves that the alternative formulae (XLIX) or (L)

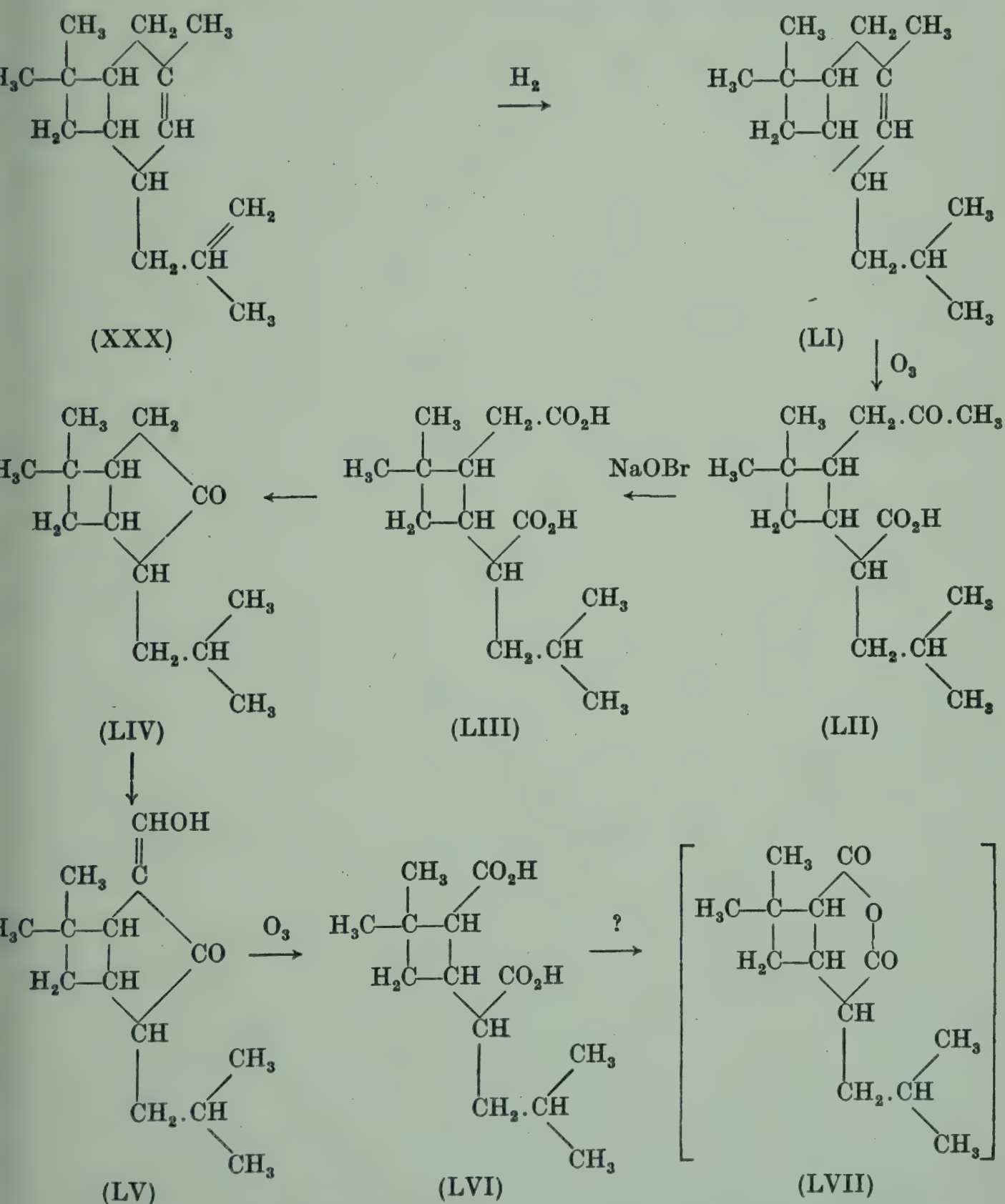


* Ruzicka, Zimmermann and Huber, *Helv. Chim. Acta*, 1936, 19, 343.

† *Chem. and Ind.* 1939, 58, 447.

suggested by Rydon* to represent the reactions of β -caryophyllene cannot be correct.

Prior to the publication of Ramage and Simonsen's communication these formulae suggested by Rydon had stimulated Ruzicka and his collaborators† to carry out an interesting investigation of the products formed by the ozonolysis of dihydro- β -caryophyllene (LI) (p. 46). In accordance with expectation this

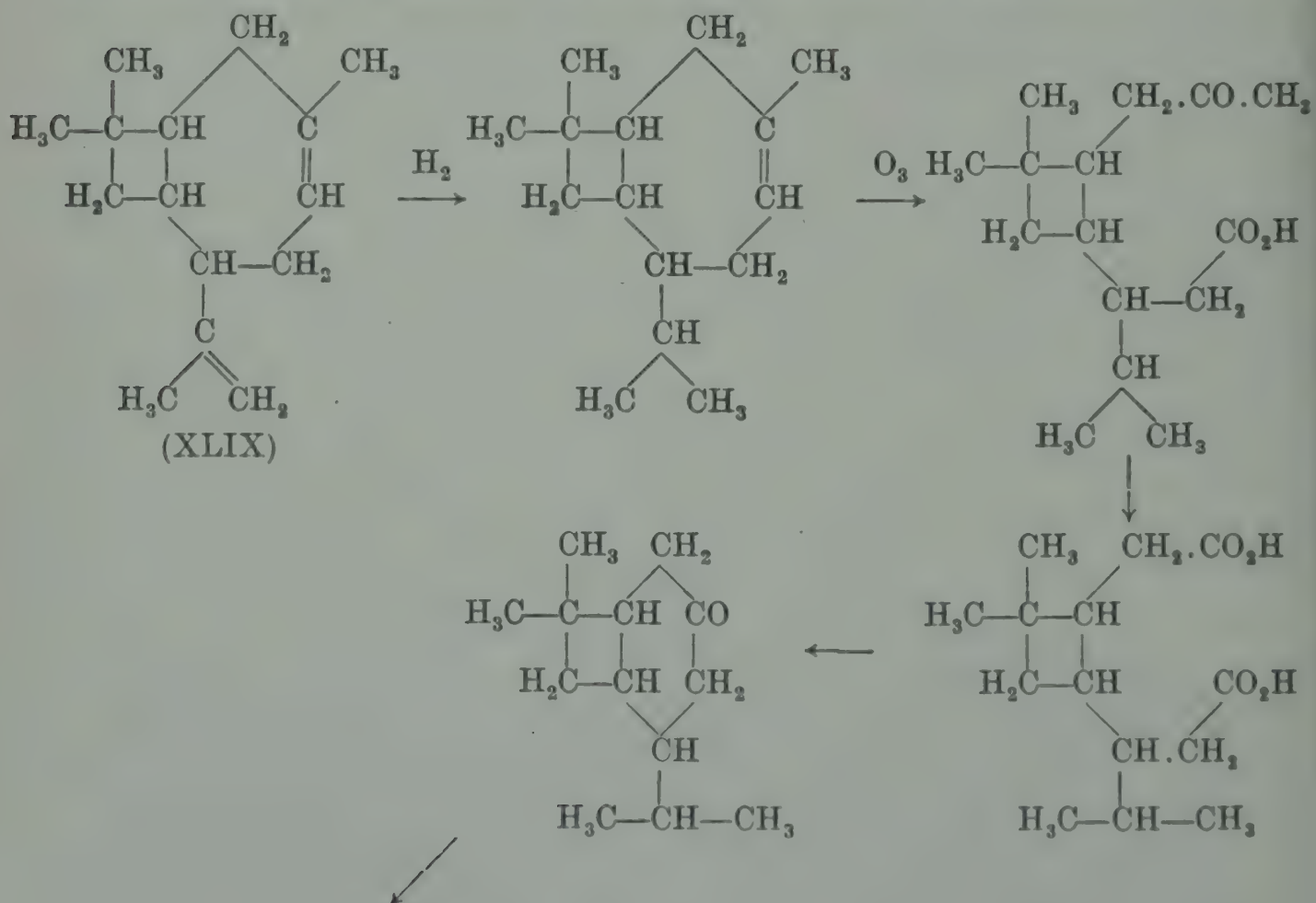


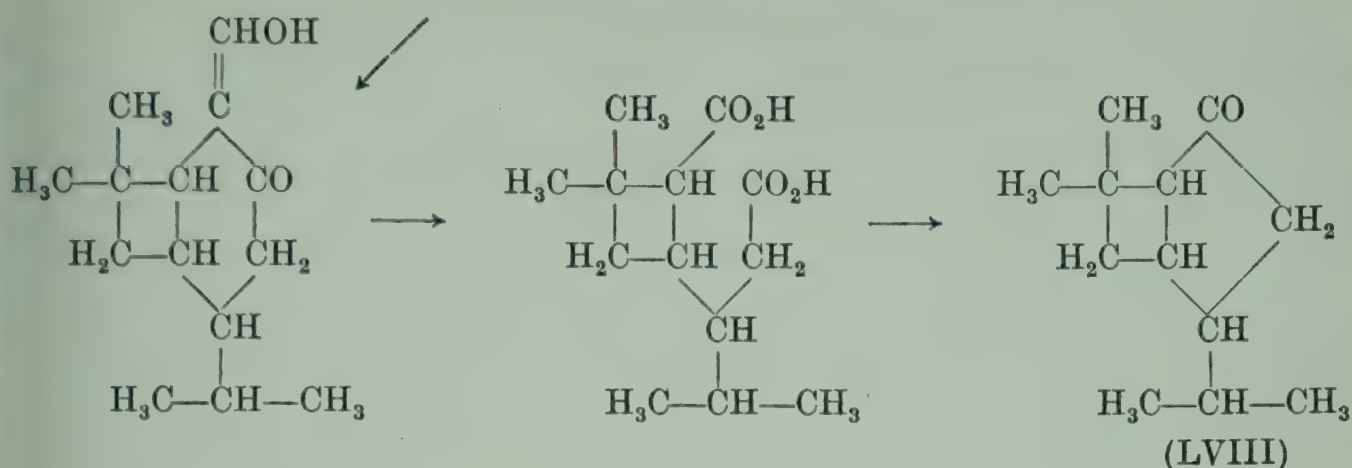
* *Ibid.* 1938, 57, 123.

† *Helv. Chim. Acta*, 1939, 22, 716.

gave a *ketonic acid*, $C_{15}H_{26}O_3$ (LII), *methyl ester*, b.p. 117–120°/1 mm., $d_4^{20^\circ}$ 0.954, $n_D^{20^\circ}$ 1.454, $\alpha_D + 47^\circ$. From this by oxidation with sodium hypobromite a *dicarboxylic acid*, $C_{14}H_{24}O_4$ (LIII), *dimethyl ester*, b.p. 106–108°/1 mm., $d_4^{20^\circ}$ 0.9924, $n_D^{20^\circ}$ 1.45, $\alpha_D + 39^\circ$, *dianilide*, m.p. 188°, was prepared. Distillation of the thorium salt of the dicarboxylic acid gave two isomeric *ketones* (LIV) $C_{13}H_{22}O$, (a) b.p. 62–63°/1 mm., $d_4^{20^\circ}$ 0.942, $n_D^{20^\circ}$ 1.4788, $\alpha_D + 44^\circ$, *semicarbazone*, m.p. 188–190°, and (b) b.p. 62–65°/1 mm., $d_4^{20^\circ}$ 0.9422, $n_D^{20^\circ}$ 1.4765, $\alpha_D - 42^\circ$, *semicarbazone*, m.p. 145°. Oxidation of the hydroxymethylene derivative (LV) of the ketone (a) gave a *dicarboxylic acid* (LVI), $C_{13}H_{22}O_4$, *dimethyl ester*, b.p. 155°/10 mm. Distillation of the thorium salt of this gave a *ketone* (LVIII) (see p. 61), $C_{12}H_{20}O$, *semicarbazone*, m.p. 153–156.5°. The relationship of the two ketones, $C_{13}H_{22}O$, to one another is not clear. The acid (LIII) should yield a ketone (LIV), the hydroxymethylene derivative (LV) of which would give on ozonolysis the dicarboxylic acid (LVI) which, assuming no molecular rearrangement, would furnish an anhydride (LVII) on distillation.

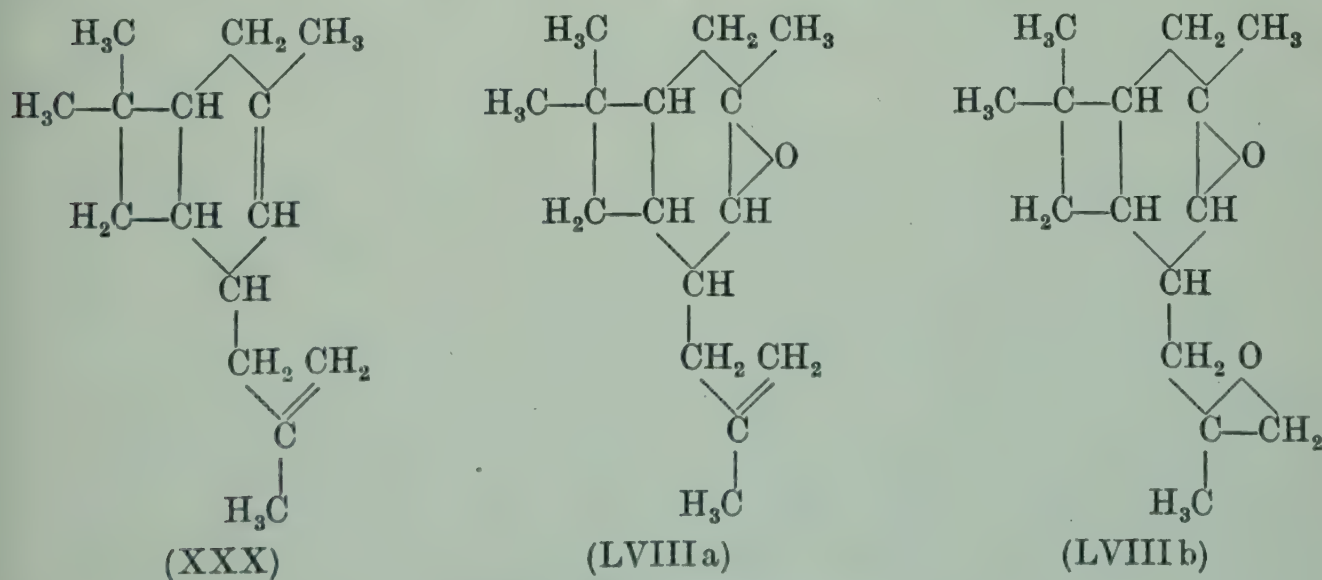
If Rydon's formula (XLIX) be, however, accepted, then the reactions would proceed in accordance with the scheme:





Since the ketone, possibly (LVIII), was only obtained in very small yield, it is doubtful if much importance can be attached to this result. We must conclude that this long series of experiments in a difficult field leads at the present time to (XXX) as the most satisfactory expression for β -caryophyllene.

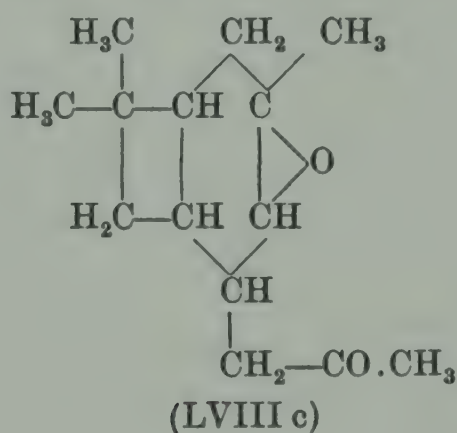
This conclusion may, however, need modification in the light of the recently reported experiments of Treibs.* Treibs found that caryophyllene was oxidised by air in the presence of a cobalt siccative catalyst to a *monoxide*, $\text{C}_{15}\text{H}_{24}\text{O}$, m.p. 64° , $d_4^{20^\circ}$ 0.9658, $n_D^{20^\circ}$ 1.4958, $[\alpha]_D^{20^\circ}$ -68° . The same monoxide was obtained by the use of one equivalent of perbenzoic acid, but if two equivalents were employed then a *dioxide*, $\text{C}_{15}\text{H}_{24}\text{O}_2$, b.p. $160^\circ/7\text{ mm.}$, $d_4^{20^\circ}$ 1.0482, $n_D^{20^\circ}$ 1.4690, $[\alpha]_D^{20^\circ}$ -42° , resulted. The monoxide was also expeditiously prepared by the action of hydrogen peroxide on caryophyllene in the presence of a vanadium catalyst. By-products from this latter method were a doubly unsaturated *alcohol*, $\text{C}_{15}\text{H}_{24}\text{O}$, b.p. $150\text{--}160^\circ/7\text{ mm.}$, $d_4^{20^\circ}$ 0.9910, $n_D^{20^\circ}$ 1.5125, $[\alpha]_D^{20^\circ}$ -34° and a *glycol*, $\text{C}_{15}\text{H}_{26}\text{O}_2$, m.p. 107° , b.p. $195\text{--}205^\circ$.



* *Chem. Ber.* 1947, 80, 56.

7 mm., $[\alpha]_D - 5^\circ$ (in alcohol), *diacetate*, m.p. 85–86°. Since caryophyllene monoxide afforded formaldehyde on ozonolysis the most reasonable formula for it, on the basis of (XXX) for caryophyllene, is (LVIIIa), whilst the dioxide must be represented by (LVIIIb).

As evidence against these formulae Treibs found that caryophyllene monoxide could be oxidised by potassium permanganate in acetone solution to a mixture of two isomeric *oxidoglycols*, $C_{15}H_{26}O_3$, α -, m.p. 141°, $[\alpha]_D^{20^\circ} - 72^\circ$ (in alcohol), β -, m.p. 119°, $[\alpha]_D^{20^\circ} - 1^\circ$ (in alcohol) and an *oxidoketone*, $C_{14}H_{22}O_2$, m.p. 61–62°, b.p. 154–158°/9 mm., $d_4^{20^\circ} 1.0339$, $n_D^{20^\circ} 1.495$, $[\alpha]_D^{20^\circ} - 124.6^\circ$ (in methanol). Although the formula (LVIIIc) might have been anticipated for this oxidoketone it was unexpectedly found that it did not give the bromoform reaction. It was suggested therefore that the side chain of caryophyllene might



consist of $\begin{array}{c} \text{CH}_2 \\ || \\ -\text{C}-\text{CH}_2\cdot\text{CH}_3 \end{array}$, giving rise to a ketone $-\text{CO}\cdot\text{CH}_2\text{CH}_3$ instead of the usually accepted *isobutenyl* side chain as in (XXX). It is, however, too early as yet to be certain that this interpretation of the oxidation evidence is the correct one.

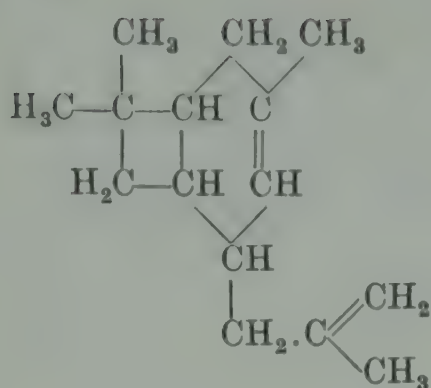
Treibs investigated a number of other reactions of caryophyllene monoxide and its derivatives. On high-pressure catalytic hydrogenation with a nickel catalyst it gave a saturated *alcohol*, $C_{15}H_{28}O$, b.p. 148–149°/9 mm., $d_4^{20^\circ} 0.9414$, $n_D^{20^\circ} 1.4919$, $[\alpha]_D^{20^\circ} - 35.3^\circ$ from which a saturated *ketone*, $C_{15}H_{26}O$, b.p. 128–130°/7 mm., $d_4^{20^\circ} 0.9463$, $n_D^{20^\circ} 1.4809$, $[\alpha]_D^{20^\circ} + 18.7^\circ$, was obtained by oxidation. Caryophyllene monoxide was rearranged by heating in aqueous dioxane solution under pressure to give a doubly unsaturated *alcohol*, $C_{15}H_{24}O$, b.p. 144–147°/7 mm., $d_4^{20^\circ} 0.9934$, $n_D^{20^\circ} 1.5143$, $[\alpha]_D^{20^\circ} - 60^\circ$ and a mono-unsaturated

ketone, $C_{15}H_{24}O$, b.p. $124-128^{\circ}/7$ mm., $d_4^{20^{\circ}} 0.9539$, $n_D^{20^{\circ}} 1.4921$, $[\alpha]_D^{20^{\circ}} -15.5^{\circ}$. The oxidoketone, $C_{14}H_{22}O_2$, mentioned above also afforded a *hydroxyketone*, $C_{14}H_{24}O_2$, b.p. $160-165^{\circ}/9$ mm., $d_4^{20^{\circ}} 1.0177$, $n_D^{20^{\circ}} 1.4973$, $[\alpha]_D^{20^{\circ}} -28^{\circ}$, on high pressure hydrogenation. By chromic acid oxidation this hydroxyketone furnished a *diketone*, $C_{14}H_{22}O_2$, b.p. $160-165^{\circ}/9$ mm., $d_4^{20^{\circ}} 1.0145$, $n_D^{20^{\circ}} 1.4909$, $[\alpha]_D^{20^{\circ}} -13.8^{\circ}$, which was not a 1:2, 1:3 or 1:4 diketone as shown by its reactions. It is not easily possible to reconcile this observation with any of the formulae suggested for caryophyllene and its interpretation must follow a further study of the chemistry of these interesting caryophyllene derivatives.

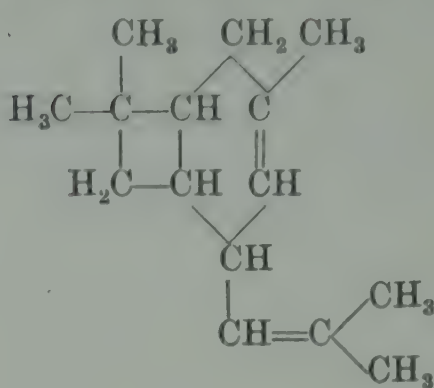
It has long been known that the β - and γ -caryophyllenes are closely related. They may be structural isomerides, as for example (XXX) and (LIX), or stereoisomerides such as (LX) and (LXI). In an attempt to elucidate this problem Ramage and Simonsen* converted γ -caryophyllene nitrosochloride by treatment with pyridine and reduction of the intermediate *oximino- γ -caryophyllene*, b.p. $162-167^{\circ}/5$ mm., into *aminodihydro- γ -caryophyllene*, $C_{15}H_{27}N$ (LXII), b.p. $147^{\circ}/13$ mm., *acetyl derivative*, b.p. $218-220^{\circ}/17$ mm. This acetyl derivative on ozonolysis gave formaldehyde and a *ketone*, $C_{16}H_{27}O_2N$ (LXIII), m.p. $139-140^{\circ}$, $[\alpha]_{5461} -58^{\circ}$ (in ethyl acetate). The formation of this ketone obviously excludes the formula (LIX) for γ -caryophyllene. The aminodihydro- γ -caryophyllene on catalytic hydrogenation gave *aminotetrahydro- γ -caryophyllene* (LXIV), b.p. $147^{\circ}/11$ mm.; treatment of this base with nitrous acid gave an alcohol, which was dehydrated with potassium bisulphate to *dihydro- γ -caryophyllene*, b.p. $140^{\circ}/24$ mm., $n_D^{16^{\circ}} 1.4921$, $\alpha_{5461} -26.1^{\circ}$, identical possibly with the hydrocarbon described by Deussen.[†] On ozonolysis this hydrocarbon gave a *ketonic acid*, $C_{15}H_{26}O_3$, without loss of any carbon atoms. Since acetamidodihydro- β -caryophyllene (p. 68) gave on ozonolysis the same ketone, $C_{16}H_{27}O_2N$ (LXIII) as did acetamidodihydro- γ -caryophyllene, it would appear possible that the β - and γ -caryophyllenes are the stereoisomerides represented by (LX) and (LXI).

* J.C.S. 1938, p. 1208.

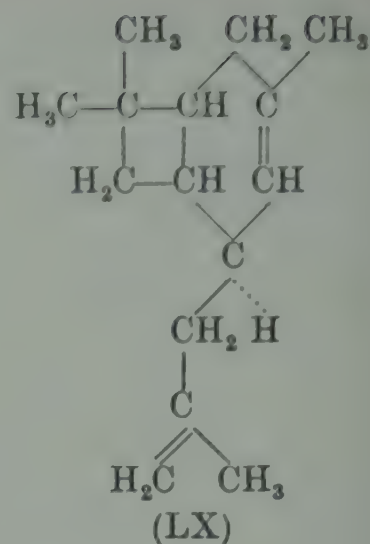
† J. pr. Chem. 1914 [ii], 90, 325.



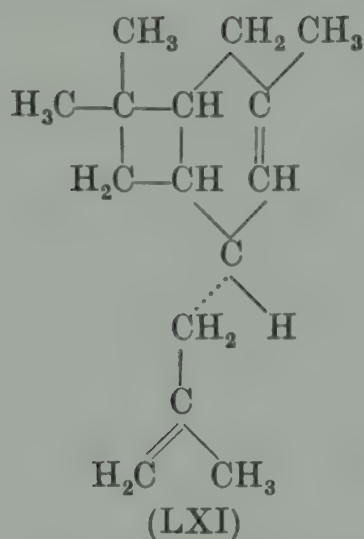
(XXX)



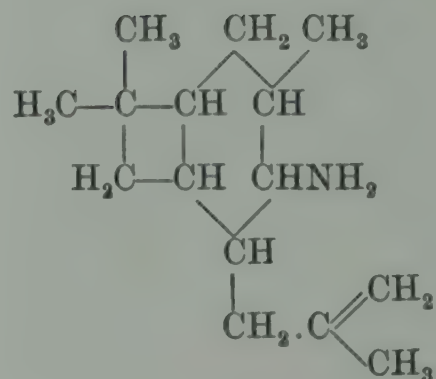
(LIX)



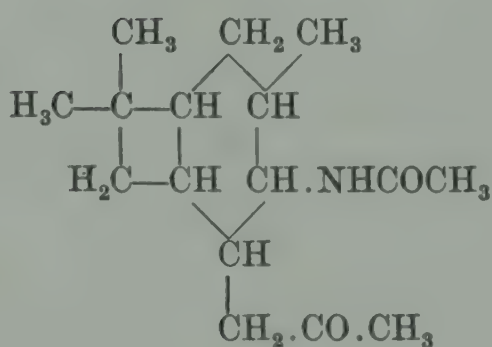
(LX)



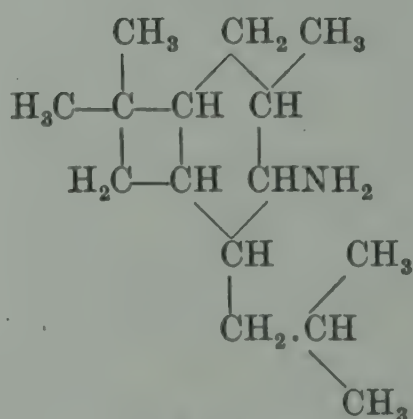
(LXI)



(LXII)



(LXIII)



(LXIV)

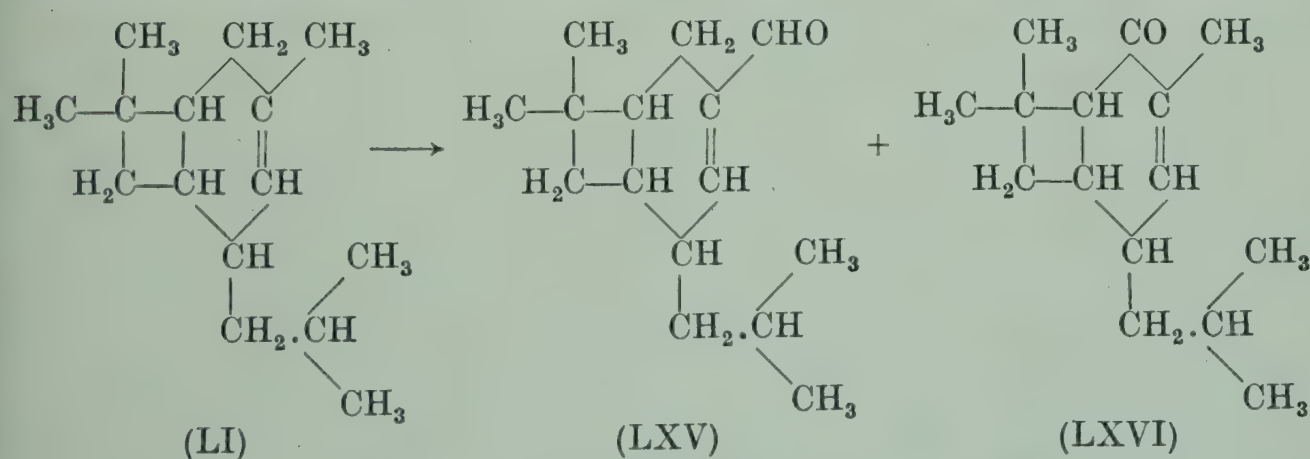
The caryophyllenes may be identified by the preparation of any of the derivatives to which reference has been made already. On hydration the sesquiterpenes yield a very characteristic product, *β*-caryophyllene alcohol, m.p. 96°. This substance is referred to on p. 67.

As was mentioned on p. 40 the only caryophyllene which has been obtained comparatively pure is *γ*-caryophyllene, the constants of which have been given on p. 41. When caryophyllene is heated at 330°, under pressure, it is decomposed, yielding a mixture of monocyclic terpenes and diterpenes.* It does not

* Semmler and Jakubowicz, *Ber.* 1914, 47, 2258.

give a naphthalene hydrocarbon when dehydrogenated with sulphur.*

The reduction of caryophyllene and the preparation from it of di- and tetra-hydrocaryophyllenes has been referred to on p. 45. When it is oxidised with potassium permanganate it yields a *glycol*, m.p. 120–120.5°,† which is probably derived from β -caryophyllene. The oxidation of dihydrocaryophyllene (LI) by selenium dioxide has been studied by Rydon,‡ Naves and Perrottet,§ Treibs,|| and by Ruzicka and his collaborators.¶ The main product of the reaction was found to be a mixture of an *aldehyde*, C₁₅H₂₄O (LXV), *semicarbazone*, m.p. 227–228°, 2:4-dinitrophenylhydrazone, m.p. 145–146° and 165–165.5°, and an isomeric *ketone* (LXVI), *semicarbazone*, m.p. 242°, $[\alpha]_D + 67.5^\circ$ (in acetic acid), 2:4-dinitrophenylhydrazone, m.p. 163–164°. By varying the conditions of the reaction a mixture of alcohols was obtained and Treibs** has described the oxidation of caryophyllene itself to a primary alcohol by this method. When dihydrocaryophyllene was oxidised with perbenzoic acid†† a mixture of oxides, C₁₅H₂₆O, (i) b.p. 134–137°/12 mm., $n_D^{18^\circ} 1.4806$, $\alpha_D^{20^\circ} - 3.38^\circ$, and (ii) b.p. 145–147°/12 mm., $n_D^{18^\circ} 1.4832$, $\alpha_D^{20^\circ} - 4.46^\circ$, resulted, whilst a third *oxide*, b.p. 120°/3 mm., $d_4^{20^\circ} 0.9488$, $n_D^{20^\circ} 1.4849$ has been prepared by Naves and Perrottet‡‡ by oxidation of the hydrocarbon with hydrogen peroxide. Attempts to convert these oxides into glycols were unsuccessful. Recently Treibs§§ has reported the preparation of yet another *dihydrocaryophyllene oxide*, m.p. 67°, b.p. 134–136°/10 mm.,



* Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, **6**, 854.

† Deussen, *Annalen*, 1912, **388**, 136.

‡ *Helv. Chim. Acta*, 1941, **24**, 789.

|| *Ber.* 1938, **71**, 1794.

** *Loc. cit.*

‡‡ *Helv. Chim. Acta*, 1941, **24**, 789.

‡ *J.C.S.* 1939, 537.

¶ *Helv. Chim. Acta*, 1939, **22**, 716.

†† Rydon, *loc. cit.*

§§ *Chem. Ber.* 1947, **80**, 56.

$[\alpha]_D^{20} - 55^\circ$ (in alcohol), obtained by the catalytic hydrogenation of caryophyllene monoxide (see p. 62). With chromyl chloride, caryophyllene forms an additive compound, $C_{15}H_{24} \cdot 2\frac{1}{2}CrO_2Cl_2$, which when decomposed by water yields (i) β -caryophyllene alcohol, (ii) a *ketone*, $C_{15}H_{24}O$, *semicarbazone*, m.p. 234° , and (iii) a *ketone* or *aldehyde*, $C_{15}H_{20}O_2$.^{*} The action of hypochlorous acid on caryophyllene has been investigated by Henderson, Robertson and Kerr.[†] They obtained a *dichlorohydrin*, $C_{15}H_{24}(OH)_2Cl_2$, which gave a liquid *monoacetate*, and which on distillation under diminished pressure was converted into an *anhydride*, $C_{15}H_{24}OCl_2$.

Caryophyllene dihydrochloride, m.p. 69° , $[\alpha]_D^{16} + 67^\circ$ (in alcoholic solution), is best prepared by the saturation of an ethereal solution of the hydrocarbon with hydrogen chloride at 0° . From this dihydrochloride a dicyclic hydrocarbon can be regenerated by careful treatment with sodium methoxide.[‡] This hydrocarbon, b.p. $121-122.5^\circ/12$ mm., $d_4^{20} 0.8996$, $n_D^{20} 1.4990$, $\alpha_D + 19^\circ$, has not been characterised by the preparation of any crystalline derivatives and its relationship to the caryophyllenes is not known. If stronger alkalis or bases, such as pyridine or quinoline, are used to remove the halogen acid, then a tricyclic hydrocarbon, b.p. $112-113^\circ/13$ mm., $d_4^{20} 0.927$, $n_D^{20} 1.50246$, $\alpha_D - 57^\circ$ is formed, which is probably identical with clovene (p. 67). When caryophyllene dihydrochloride is warmed with silver acetate in acetic acid solution a mixture of (i) a *hydrocarbon* yielding the same dihydrochloride on treatment with hydrogen chloride, (ii) a dicyclic sesquiterpene *alcohol*, $C_{15}H_{26}O$, and (iii) a *glycol*, $C_{15}H_{26}(OH)_2$, m.p. 175° , is obtained.[§]

On treatment of caryophyllene with hydrogen chloride, Bell and Henderson^{||} have found that, in addition to the dihydrochloride, a liquid *monohydrochloride* is formed, the acid having caused ring closure to occur. When this hydrochloride is warmed with silver acetate in acetic acid solution, it yields a tricyclic hydrocarbon probably identical with clovene, and the acetate of a tricyclic *alcohol*. The latter, which is obtained on hydrolysis

^{*} Gibson, Robertson and Sword, *J.C.S.* 1926, p. 164.

[†] *J.C.S.* 1926, p. 69.

[‡] *Inter al.* Semmler and Mayer, *Ber.* 1910, 43, 3451.

[§] Henderson, Robertson and Kerr, *J.C.S.* 1926, p. 67.

^{||} *Ibid.* 1930, p. 1971.

of the acetate, boils at $146\text{--}154^\circ/10\text{ mm.}$, $d_4^{17^\circ} 0.9934$, $n_D^{17^\circ} 1.5039$. It is apparently isomeric with α - and β -caryophyllene alcohols and, on dehydration with phosphorus pentoxide, gives clovene.

By the hydration of caryophyllene with the Bertram-Wallach reagent, Wallach and Walker* prepared β -caryophyllene alcohol (isocaryophyllene alcohol), m.p. 96° , b.p. $287\text{--}289^\circ$, phenylurethane, m.p. $136\text{--}137^\circ$. This alcohol, which is extremely stable, is undoubtedly tricyclic and no longer contains the caryophyllene nucleus. It gives with phosphorus pentachloride a chloride, $\text{C}_{15}\text{H}_{25}\text{Cl}$, m.p. 63° , the corresponding bromide melting at $61\text{--}62^\circ$ and the iodide at 61° . Like the alcohol, this chloride is extremely stable and it is not acted upon by sodium methoxide but with silver acetate in acetic acid solution it yields the acetate of β -caryophyllene alcohol, m.p. 40° , b.p. $149\text{--}152^\circ/10\text{ mm.}$, $d_4^{17^\circ} 1.003$, $n_D^{17^\circ} 1.4919$, the corresponding formate, b.p. $141\text{--}145^\circ/10\text{ mm.}$, $d_4^{17^\circ} 1.029$, $n_D^{17^\circ} 1.4998$, $[\alpha]_{5461}^{17^\circ} -10.46^\circ$, being obtained when the alcohol is digested with formic acid.† When β -caryophyllene alcohol is heated with zinc dust under pressure isodihydrocaryophyllene, $\text{C}_{15}\text{H}_{26}$, b.p. $137\text{--}138^\circ/19\text{ mm.}$, $d_4^{20^\circ} 0.919$, $n_D 1.4925$, is formed; this is probably a saturated tricyclic hydrocarbon.‡ By the dehydration of β -caryophyllene alcohol with phosphorus pentoxide, Wallach and Walker obtained a tricyclic hydrocarbon, clovene, b.p. $111\text{--}113^\circ/10\text{ mm.}$, $d_4^{20^\circ} 0.924$, $n_D^{20^\circ} 1.4980$, $\alpha_D +1.3^\circ$. This hydrocarbon is formed also as a by-product in the hydration of caryophyllene. Clovene has not been characterised by the preparation of any crystalline derivatives. It has been observed by Henderson, McCrone and Robertson§ that the hydrocarbon prepared by the dehydration of β -caryophyllene alcohol is not homogeneous, but can be separated by distillation into clovene and isoclovene, b.p. $130\text{--}131^\circ/12\text{ mm.}$, $d_4^{19^\circ} 0.843$, $n_D^{19^\circ} 1.5039$, $[\alpha]_D -56.6^\circ$, which yields a crystalline hydrochloride, m.p. 87° , hydrobromide, m.p. 75° . These differ completely from the isomeric clovene derivatives prepared by the action of the phosphorus halides on β -caryophyllene alcohol. When isoclovene hydrochloride is treated with silver acetate and the product hydrolysed, isoclovene alcohol,

* *Annalen*, 1892, 271, 288.

† Robertson, Kerr and Henderson, *J.C.S.* 1925, 127, 1944; 1926, p. 64.

‡ Semmler, *Ber.* 1903, 36, 1038.

§ *J.C.S.* 1929, p. 1371.

m.p. 98° , $[\alpha]_D + 227^{\circ}$, is obtained. This is probably a tertiary alcohol, since it does not react with phenyl isocyanate and it is readily dehydrated. By the oxidation of clovene with chromic acid Ruzicka and Gibson* have obtained an acid, *clovenic acid*, $C_{15}H_{24}O_4$, m.p. 182° , yielding an *anhydride*, m.p. $50-51^{\circ}$. Clovenic acid is extraordinarily resistant to oxidising agents† and cannot be brominated. Both carboxyl groups are probably attached therefore to quaternary carbon atoms; its relationship to the caryophyllenes is obscure.

Asahina and Tsukamoto‡ have found that if caryophyllene is hydrated with Aschan's reagent (sulphuric acid monohydrate in ethereal solution) then, in addition to β -caryophyllene alcohol, a second alcohol, α -caryophyllene alcohol, m.p. 117° , b.p. $143-152^{\circ}/10$ mm., $d_4^{17^{\circ}} 0.9860$, $n_D^{17^{\circ}} 1.5010$, *phenylurethane*, m.p. 180° is formed. The relationship of the three tricyclic alcohols, α - and β -caryophyllene alcohols and isoclovene alcohol, to one another has not been determined and it is not known whether they are structural or stereoisomerides. On dehydration, α -caryophyllene alcohol yields clovene but no isoclovene, and it differs also from the β -alcohol in its behaviour to Beckmann's chromic acid mixture. With this reagent α -caryophyllene alcohol yields a crystalline *acid*, $C_{15}H_{24}O_4$, m.p. 187° , *anhydride*, m.p. 49.5° , identical probably with clovenic acid, whilst the β -alcohol gives a liquid *acid*, $C_{10}H_{12}O_3$.§

When β -caryophyllene nitrosite is reduced with sodium and alcohol, *aminodihydro- β -caryophyllene*, $C_{15}H_{27}N$, b.p. $138-143^{\circ}/2$ mm., $d_{25}^{25^{\circ}} 0.9293$, $n_D^{17^{\circ}} 1.5030$, $[\alpha]_{5461} + 13.5^{\circ}$, *acetyl derivative*, b.p. $220-222^{\circ}/18$ mm., *3:5-dinitrobenzoate*, m.p. $172-173^{\circ}$, is obtained.|| This base is further reduced by catalytic hydrogenation to *aminotetrahydro- β -caryophyllene*, $C_{15}H_{29}N$, b.p. $140-142^{\circ}/12$ mm., $d_{20}^{20^{\circ}} 0.9194$, $n_D^{15^{\circ}} 1.4956$, $[\alpha]_{5461} - 29.1^{\circ}$.

When caryophyllene in benzene solution is treated with maleic anhydride an *adduct*, $C_{19}H_{26}O_3$ (LXVII), m.p. 98° , $[\alpha]_D + 28^{\circ}$ (in alcohol), $[\alpha]_D + 49^{\circ}$ (in chloroform), is formed.¶ In a further

* *Helv. Chim. Acta*, 1931, 14, 570.

† Blair, *J.C.S.* 1935, p. 1297.

‡ *J. Pharm. Soc. Japan*, 1922, p. 463.

§ Bell and Henderson, *J.C.S.* 1930, p. 1975.

|| Ramage and Simonsen, *J.C.S.* 1934, p. 1806.

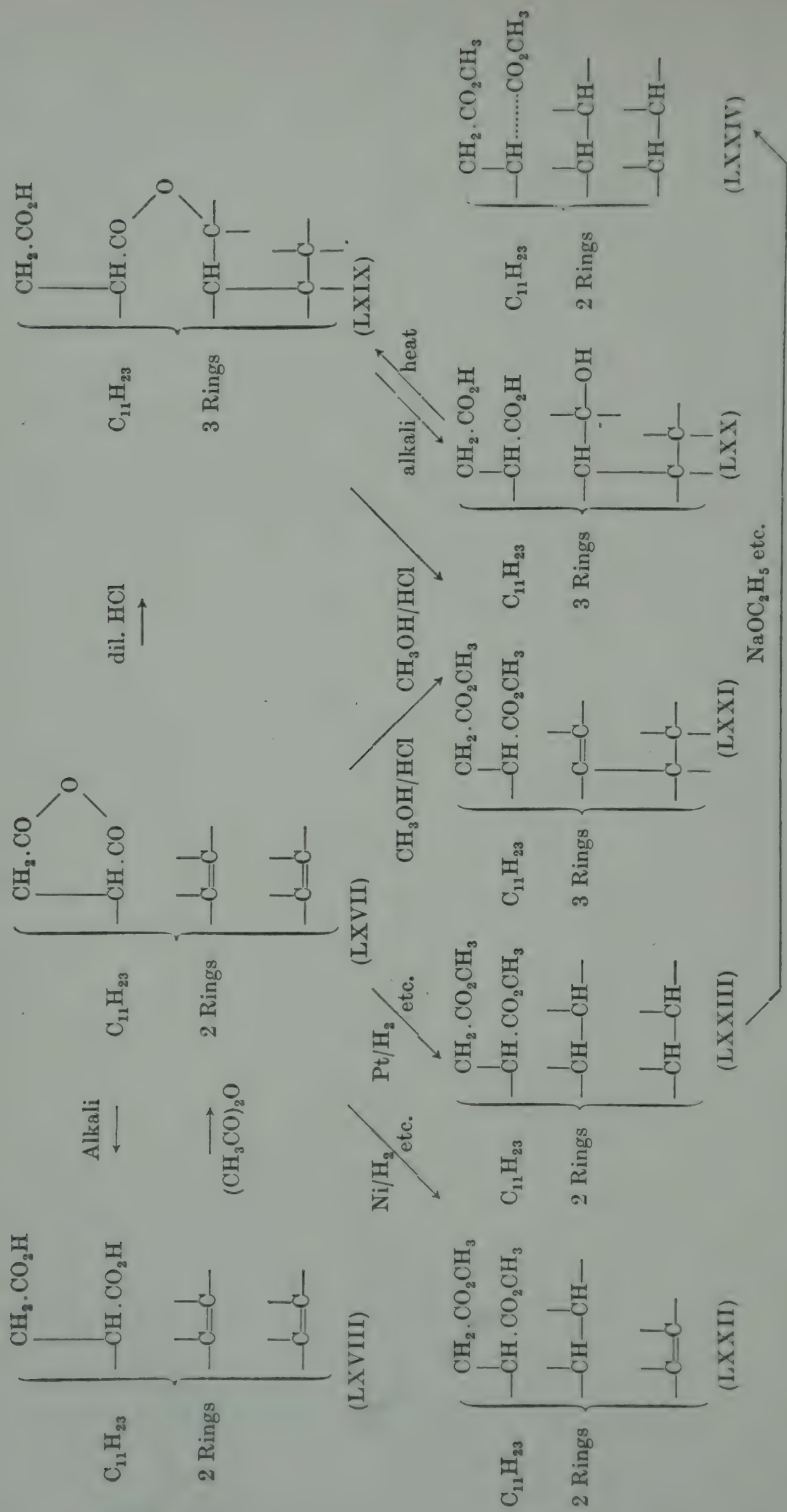
¶ Ruzicka and Zimmermann, *Helv. Chim. Acta*, 1935, 18, 219.

investigation of the adduct, Ruzicka, Plattner and Balla* observed that some specimens of caryophyllene furnish good yields of the adduct, whilst others do not react at all. This behaviour was taken as evidence of the heterogeneity of the original caryophyllene, and the enhanced yields of caryophyllene dihydrochloride obtained from the non-reacting hydrocarbons as well as changes in optical rotatory power supported this view. The maleic anhydride adduct is not formed according to the usual Diels-Alder addition scheme, but by allylic substitution.† On hydrolysis with dilute alkali it yields an unsaturated *dicarboxylic acid* (LXVIII), *dimethyl ester*, b.p. $150^{\circ}/1\text{ mm.}$; $d_4^{20^{\circ}} 1.0439$, $n_D^{20^{\circ}} 1.4940$, $[\alpha]_D + 32^{\circ}$ (in alcohol), from which the original adduct is regenerated by the action of acetic anhydride, whilst on heating the adduct with dilute hydrochloric acid a saturated *lactonic acid*, $\text{C}_{19}\text{H}_{28}\text{O}_4$ (LXIX), m.p. 208° , *monomethyl ester*, m.p. 156° , $[\alpha]_D - 48.1^{\circ}$ (in benzene) is obtained. This latter ester is hydrolysed by alcoholic potassium hydroxide to a saturated *hydroxydicarboxylic acid* (LXX), m.p. *ca.* 160° , $[\alpha]_D - 24.1^{\circ}$ (in alcohol), easily reconverted to the parent lactonic acid by heating above its melting point. With hot methanolic hydrochloric acid both the original adduct (LXVII) and the lactonic acid (LXIX) furnish an unsaturated *dimethyl ester* (LXXI), $\text{C}_{21}\text{H}_{32}\text{O}_4$, b.p. $165^{\circ}/1\text{ mm.}$, $[\alpha]_D - 193^{\circ}$ to -201° (in alcohol),‡ from which by alkaline hydrolysis a *dicarboxylic acid*, $\text{C}_{19}\text{H}_{28}\text{O}_4$, m.p. 173° , $[\alpha]_D - 217^{\circ}$ (in alcohol) could be prepared. Catalytic hydrogenation of the primary adduct (LXVII) in the presence of Raney nickel in alcoholic solution led to the uptake of one molecular proportion of hydrogen, and the formation of the anhydride of an unsaturated *dicarboxylic acid*, *dimethyl ester* (LXXII), $\text{C}_{21}\text{H}_{34}\text{O}_4$, b.p. $150^{\circ}/1\text{ mm.}$, $d_4^{20^{\circ}} 1.0418$, $n_D^{20^{\circ}} 1.4937$, $[\alpha]_D + 33.6^{\circ}$ (in alcohol). However, by catalytic reduction in acetic acid solution, two molecular proportions of hydrogen were absorbed and the anhydride of a saturated *dicarboxylic acid*, *dimethyl ester*, $\text{C}_{21}\text{H}_{36}\text{O}_4$ (LXXIII), b.p. $160^{\circ}/1\text{ mm.}$, $d_4^{20^{\circ}} 1.0211$, $n_D^{20^{\circ}} 1.4819$, $[\alpha]_D - 18^{\circ}$ (in alcohol), *dianilide*, m.p. 222° , $[\alpha]_D - 28^{\circ}$ (in acetone), resulted. By hydrolysis of this latter dimethyl ester

* *Ibid.* 1941, 24, 1219.

† Compare Alder, Paseler and Schmitz, *Ber.* 1943, 76, 27.

‡ Compare Goodway and West, *J.C.S.* 1939, p. 1853.



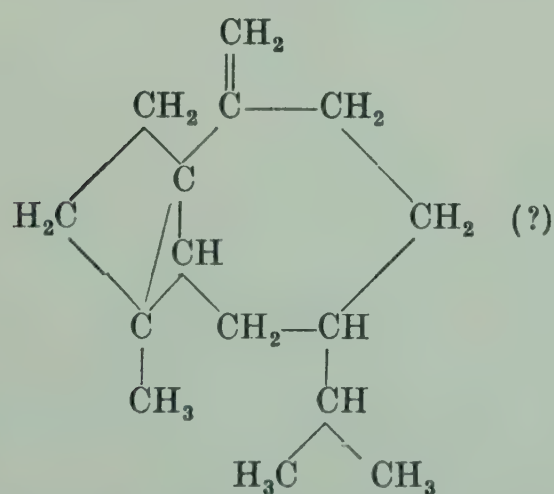
(LXXIII) with sodium ethoxide and re-esterification a stereoisomeric *dimethyl ester* (LXXIV), b.p. $160^{\circ}/1$ mm., $d_4^{20^{\circ}}$ 1.0214, $n_D^{20^{\circ}}$ 1.4796, $[\alpha]_D + 0.9^{\circ}$ (in alcohol), *dianilide*, m.p. 229° , $[\alpha]_D + 44^{\circ}$ (in acetone) could be obtained.

Caryophyllene reacts in a similar manner with diethyl acetylenedicarboxylate and with diethyl azodicarboxylate.* With the former reagent the *adduct*, $C_{21}H_{30}O_4$, had b.p. $170-180^{\circ}/1$ mm., $d_4^{21.6^{\circ}}$ 1.0542, $n_D^{21.6^{\circ}}$ 1.5063, $[\alpha]_D + 79.3^{\circ}$ (in chloroform) and gave on alkaline hydrolysis a *dicarboxylic acid*, m.p. $122-123^{\circ}$, $[\alpha]_D + 77.2^{\circ}$ (in chloroform), which could be hydrogenated to the dicarboxylic acid corresponding to the ester (LXXIV) obtained from the maleic anhydride adduct. The *adduct*, from caryophyllene and diethyl azodicarboxylate, $C_{21}H_{34}O_4N_2$, had m.p. 139° , $[\alpha]_D + 39^{\circ}$ (in chloroform). Plattner and Werner suggest that the varying yields of the maleic anhydride adduct may be due, not to the heterogeneity of the caryophyllene used as mentioned above, but to the catalysis or inhibition of the allylic substitution by impurities.

Caryophyllene reacts with ethyl diazoacetate to give a *cyclopropane ester* from which, by hydrolysis, an *acid* $C_{16}H_{25}.CO_2H$, m.p. 165° , $[\alpha]_{5461} - 40^{\circ}$, can be prepared. It does not appear to have been determined from which caryophyllene this condensation product is derived, and, since it is extremely resistant to potassium permanganate, it is not improbably a derivative of clovene.†

C. TRICYCLIC HYDROCARBONS

AROMADENDRENE



* Plattner and Werner, *Helv. Chim. Acta*, 1944, **27**, 1010.

† Deussen, *J. pr. Chem.* 1927 [ii], **117**, 282; Gibson, *J.C.S.* 1928, p. 750.

According to Smith* aromadendrene is the principal sesquiterpene occurring in the eucalyptus oils. It is probably present also in a number of other oils.†

Aromadendrene, $C_{15}H_{24}$, has b.p. $121^{\circ}/10$ mm., $d_4^{20^{\circ}}$ 0.9116, $n_D^{20^{\circ}}$ 1.4978, $[\alpha]_{5770}^{20^{\circ}} - 6.1^{\circ}$, $[R_L]_D$ 64.89 (calc. for a dicyclic sesquiterpene 66.14, for a tricyclic sesquiterpene 64.40). It is easily reduced by catalytic hydrogenation with uptake of one molecular proportion of hydrogen to give *dihydroaromadendrene*, $C_{15}H_{26}$, b.p. $121-122^{\circ}/10$ mm., $d_4^{17^{\circ}}$ 0.9014, $n_D^{17^{\circ}}$ 1.4871. Dihydroaromadendrene behaves as a saturated hydrocarbon, so that the parent aromadendrene must be a tricyclic, monoethenoid sesquiterpene. The double bond of aromadendrene must be present as an exocyclic methylene group for, on ozonolysis, formaldehyde and a saturated ketone, *aromadendrone*, $C_{14}H_{22}O$, m.p. $84.5-85^{\circ}$, $[\alpha]_{5770}^{20^{\circ}} + 5.4^{\circ}$ (in alcohol), *oxime*, m.p. 103° , *semicarbazone*, m.p.s. $195-196^{\circ}$ and $201.5-202.5^{\circ}$, *p-nitrophenylhydrazone*, m.p. 131° , *benzylidene* derivative, m.p. $66-66.5^{\circ}$, were obtained. Aromadendrone, together with *aromadendrene glycol*, $C_{15}H_{26}O_2$, m.p. 118° , results also from the oxidation with potassium permanganate of aromadendrene.‡ The glycol gave aromadendrone on further oxidation with the same reagent.

It was observed by Pfau and Plattner§ that on dehydrogenation of aromadendrene with sulphur S-guaiazulene (I) (see p. 156) was formed. Consideration of the physical constants, more especially the exaltation of the molecular refraction, suggested that the sesquiterpene contained a *cyclopropane* ring in conjugation with the ethylenic linkage. The parachors, Raman spectra and other physical properties of aromadendrene and its derivatives were also in agreement with this view.

Some very recent work by Treibs and Barchet|| has thrown considerable light on the question of the constitution of aromadendrene. Aromadendrone was reduced by sodium and alcohol to *aromadendrol*, m.p. 62° , b.p. $158-160^{\circ}/15$ mm., $[\alpha]_D^{20^{\circ}} - 44.9^{\circ}$, which on dehydration by heating with boric acid afforded *apo-*

* Baker and Smith, *A Research on the Eucalypts*, 1920, p. 416.

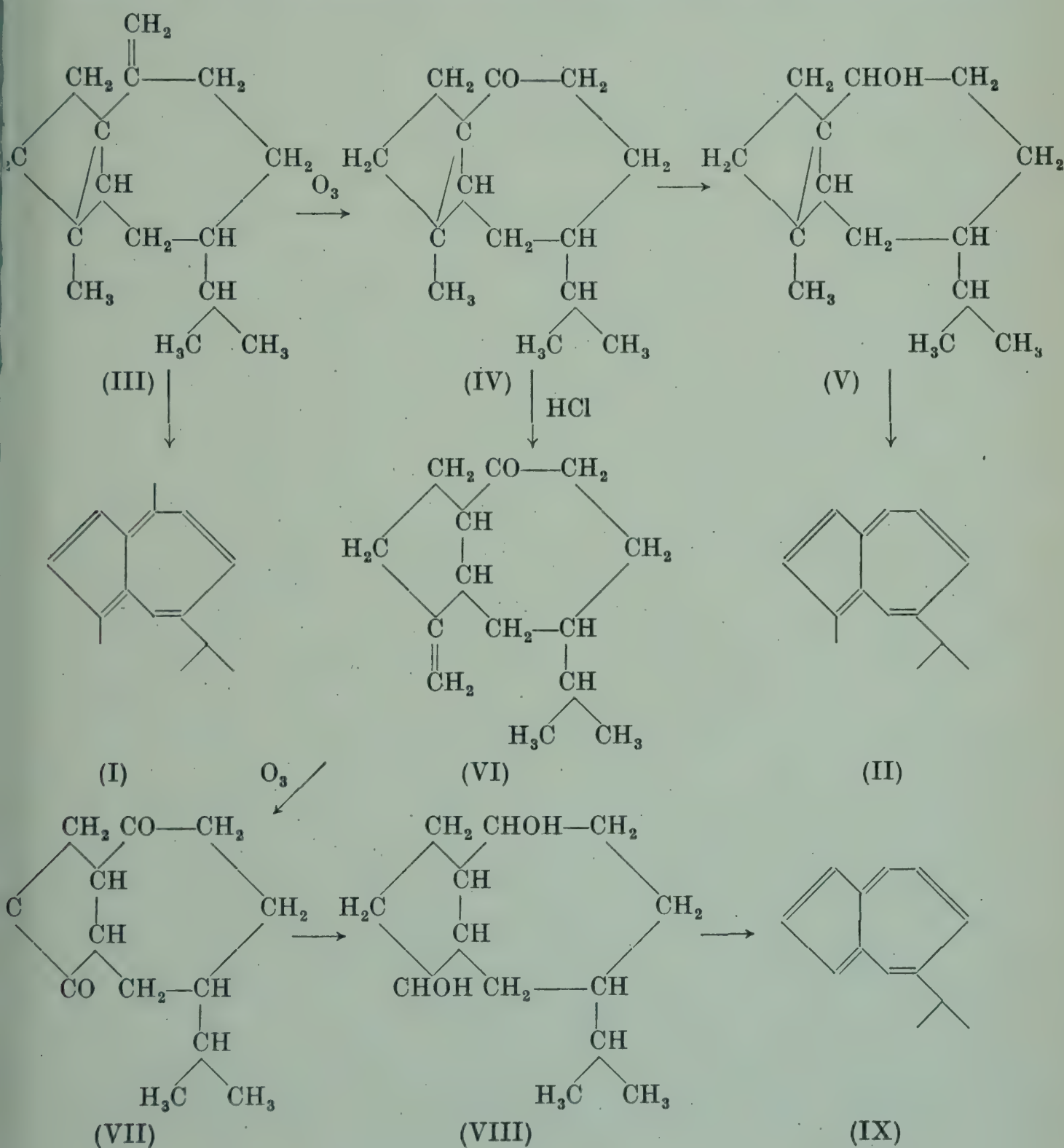
† Briggs and Short, *J.C.S.* 1928, p. 2524; compare Naves and Perrottet, *Helv. Chim. Acta*, 1940, **23**, 912.

‡ Radcliffe and Short, *J.C.S.* 1938, p. 1200.

§ *Helv. Chim. Acta*, 1936, **19**, 871; compare Radcliffe and Short, *loc. cit.*

|| *Annalen*, 1950, **566**, 89.

aromadendrene, $C_{14}H_{22}$, b.p. $118-120^{\circ}/15$ mm., $d_4^{20^{\circ}}$ 0.9147, $n_D^{20^{\circ}}$ 1.5040, $[\alpha]_D^{20^{\circ}}$ $+41.5^{\circ}$. Dehydrogenation of this hydrocarbon by selenium gave the blue 1-methyl-7-isopropylazulene (II) (*trinitrobenzene adduct*, $C_{20}H_{19}O_6N_3$, m.p. 141°). The assignment of constitution to this azulene depended upon a prior knowledge of the structure of S-guaiazulene and upon a careful consideration of the absorption spectrum of the compound. These experiments show that the exocyclic methylene grouping of *aromadendrene* must be attached to position four in the azulene skeleton. Formula (III) is a suitable vehicle for the expression of this and



other facts mentioned above. Aromadendrone would then be represented by (IV) and aromadendrol by (V).

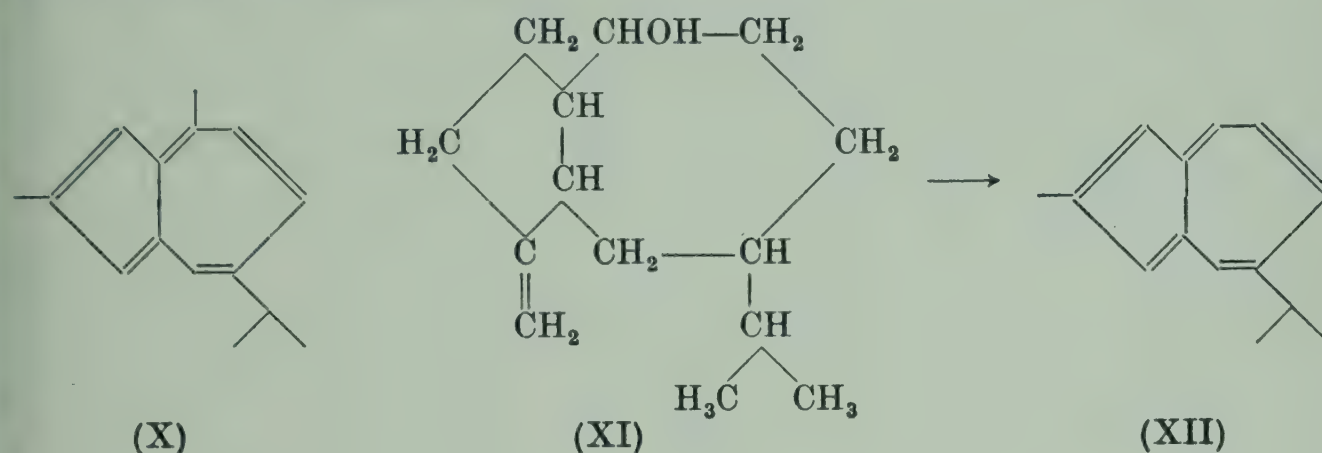
On treatment with hydrogen chloride the *cyclopropane* ring of aromadendrone was broken to give *isoaromadendrone*, $C_{14}H_{22}O$ (VI), m.p. 60° , $[\alpha]_D^{20^\circ} -49.0^\circ$. This ketone also possessed an exocyclic methylene grouping, for on ozonolysis a diketone, $C_{13}H_{20}O_2$ (VII), m.p. 98° , b.p. $193-202^\circ/15\text{ mm.}$, $[\alpha]_D -30.6^\circ$, *dioxime*, m.p. 213° , was obtained. Reduction of this diketone by sodium and alcohol afforded the corresponding *glycol*, $C_{13}H_{24}O_2$ (VIII), b.p. $194-198^\circ/15\text{ mm.}$, $d_4^{20^\circ} 1.0825$, $n_D^{20^\circ} 1.5184$, $[\alpha]_D^{20^\circ} -25.2^\circ$, dehydrated by boric acid to the *diene*, $C_{13}H_{20}$, b.p. $126-128^\circ/19\text{ mm.}$, $d_4^{20^\circ} 0.9360$, $n_D^{20^\circ} 1.5097$, $[\alpha]_D^{20^\circ} -32.5^\circ$, from which 7-isopropylazulene (IX) (*trinitrobenzene adduct*, $C_{19}H_{17}O_6N_3$, m.p. 134°), was obtained by dehydrogenation with selenium.

Although these experiments are best interpreted by formula (III) it should be noted that this expression is novel in that it contains a three-membered ring fused into a five-membered ring. It must represent a highly strained structure and further evidence as to the constitution of aromadendrene is required before (III) can be regarded as established beyond doubt.

Treibs and Barchet,* during the course of the work summarised briefly above, made several interesting observations on the dehydrogenation of aromadendrene and of the *isoaromadendrene*, $C_{15}H_{24}$, b.p. $140-145^\circ/17\text{ mm.}$, $d_4^{20^\circ} 0.9210$, $n_D^{20^\circ} 1.5075$, $[\alpha]_D^{20^\circ} -53.2^\circ$, obtained therefrom by treatment with hydrogen chloride followed by dehydrochlorination of the resulting dichloride by alkali. It was discovered that both hydrocarbons gave S-guaiazulene (I) or Se-guaiazulene (probably (X), see p. 163), depending on the temperature used for dehydrogenation rather than the reagent. The higher the temperature the greater the likelihood of the formation of the Se-guaiazulene with the rearranged carbon skeleton. Similarly it was found that reduction of *isoaromadendrone* (VI) by sodium and alcohol to the *alcohol* (XI), $C_{14}H_{24}O$, m.p. 85° , b.p. $165-167^\circ/19\text{ mm.}$, $[\alpha]_D^{20^\circ} -48.1^\circ$, followed by dehydration to the hydrocarbon *isoapoaromadendrene*, $C_{14}H_{22}$, b.p. $121^\circ/17\text{ mm.}$, $d_4^{20^\circ} 0.9229$, $n_D^{20^\circ} 1.5034$, $[\alpha]_D^{20^\circ} -18.7$, and dehydrogenation of the latter by selenium

* *Loc. cit.*

under high temperature conditions, gave not 1-methyl-7-isopropylazulene (II) but the violet 2-methyl-7-isopropylazulene (XII) (*trinitrobenzene adduct*, $C_{20}H_{19}O_6N_3$, m.p. 127°). The formation of the latter is attended by a migration of the methyl group from the one to the thermodynamically more stable two position of the azulene skeleton.



CEDRENE

Cedrene, $C_{15}H_{24}$, occurs in cedar wood oil (from *Juniperus virginiana*) and it was first isolated from this oil by Walter.* At the same time he prepared a hydrocarbon having very similar properties by the dehydration of the alcohol, cedrol (cedar wood camphor). Naturally occurring cedrene is a mixture in which α -cedrene is the main constituent. β -Cedrene and some unidentified sesquiterpenes are also present.† The “synthetic” cedrene, prepared by dehydration of cedrol (p. 170), is essentially pure α -cedrene and it is this material which has been used in the more recent experiments for the determination of the structure of the hydrocarbon.

Pure α -cedrene prepared by dehydration of cedrol with formic acid is a colourless somewhat viscid oil, b.p. $100^\circ/3.5 \text{ mm.}$, $d_4^{20^\circ} 0.9342$, $n_D^{20^\circ} 1.4982$, $[\alpha]_D^{20^\circ} -91.3^\circ$, whereas a typical specimen of natural cedrene had b.p. $121^\circ/12 \text{ mm.}$, $d_4^{17^\circ} 0.9367$, $n_D^{17^\circ} 1.5030$, $[\alpha]_D -56.3^\circ$. Specimens of cedrene prepared from cedrenone semicarbazone or from cedrenene always have a lower rotatory power than those obtained by dehydration of cedrol and, therefore, are less pure.‡ Indeed the measurement of the optical

* *Annalen*, 1841, **39**, 247; 1843, **48**, 35; *Ann. Chim.* 1843 [iii], **1**, 498; 1844 [iii], **8**, 854.

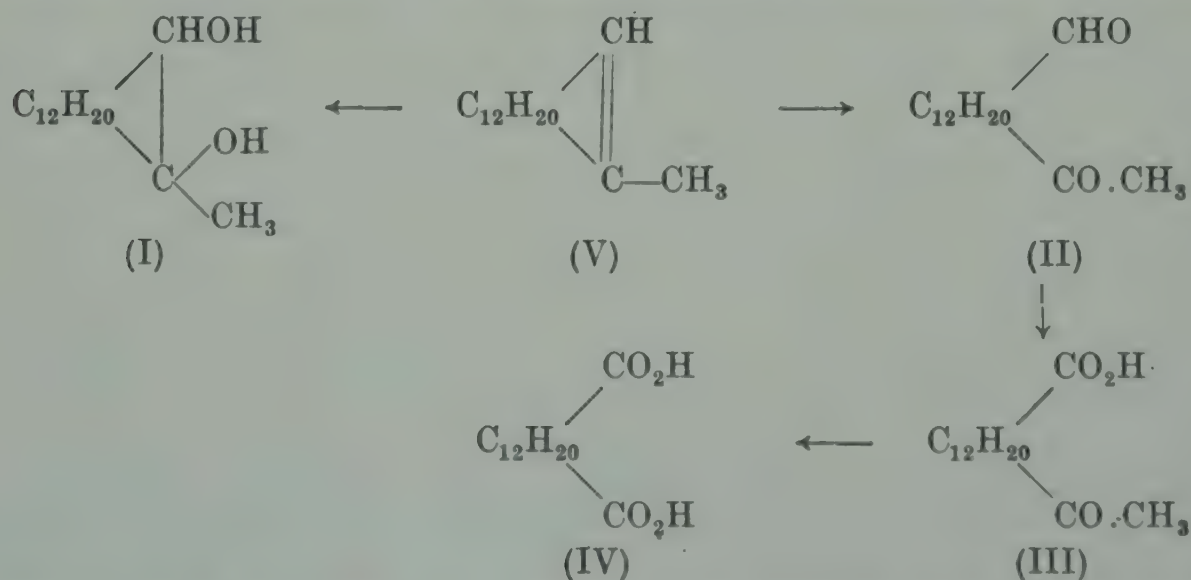
† Naves, Papazian and Perrottet, *Helv. Chim. Acta*, 1943, **26**, 302.

‡ Blumann and Schulz, *Ber.* 1931, **64**, 1540.

rotatory power of a sample of α -cedrene is probably the best criterion of its purity. It was deduced from the molecular refraction of cedrene that the hydrocarbon was probably tricyclic and possessed one double bond. These conclusions have been amply confirmed by the many experiments discussed below.

By the oxidation of α -cedrene or of naturally occurring cedrene with potassium permanganate in acetone solution three products could be characterised.* The first a *glycol*, $C_{15}H_{26}O_2$ (I), m.p. 160° , b.p. $186-187^\circ/12$ mm., $d^{15^\circ} 1.053$, the second a *ketonic aldehyde*, $C_{15}H_{24}O_2$ (II), b.p. $165^\circ/10$ mm., $d^{15^\circ} 1.055$, *disemicarbazone*, m.p. 234° , and the third a liquid *ketonic acid*, $C_{15}H_{24}O_3$ (III), b.p. $200-215^\circ/10$ mm., *semicarbazone*, m.p. 162° , *methyl ester*, b.p. $165-170^\circ/10$ mm., $d^{20^\circ} 1.0509$, $n_D^{20^\circ} 1.4882$, $\alpha_D -32.24^\circ$. The ketonic acid was easily oxidised by sodium hypobromite to a dibasic acid, *cedrenedicarboxylic acid*, $C_{14}H_{22}O_4$ (IV), m.p. 182.5° , *dimethyl ester*, b.p. $179-182.5^\circ/12$ mm., $d^{20^\circ} 1.0732$, $n_D 1.4814$, $\alpha_D -36.24^\circ$. The ketonic acid (III) can be prepared very easily by the ozonolysis of α -cedrene and this provides a convenient method for the characterisation of the sesquiterpene.† These oxidation reactions are most simply interpreted by the partial formulae given below, the oxidation of α -cedrene (V), to cedrenedicarboxylic acid being comparable to the oxidation of α -pinene to pinic acid (see Vol. II, p. 115).

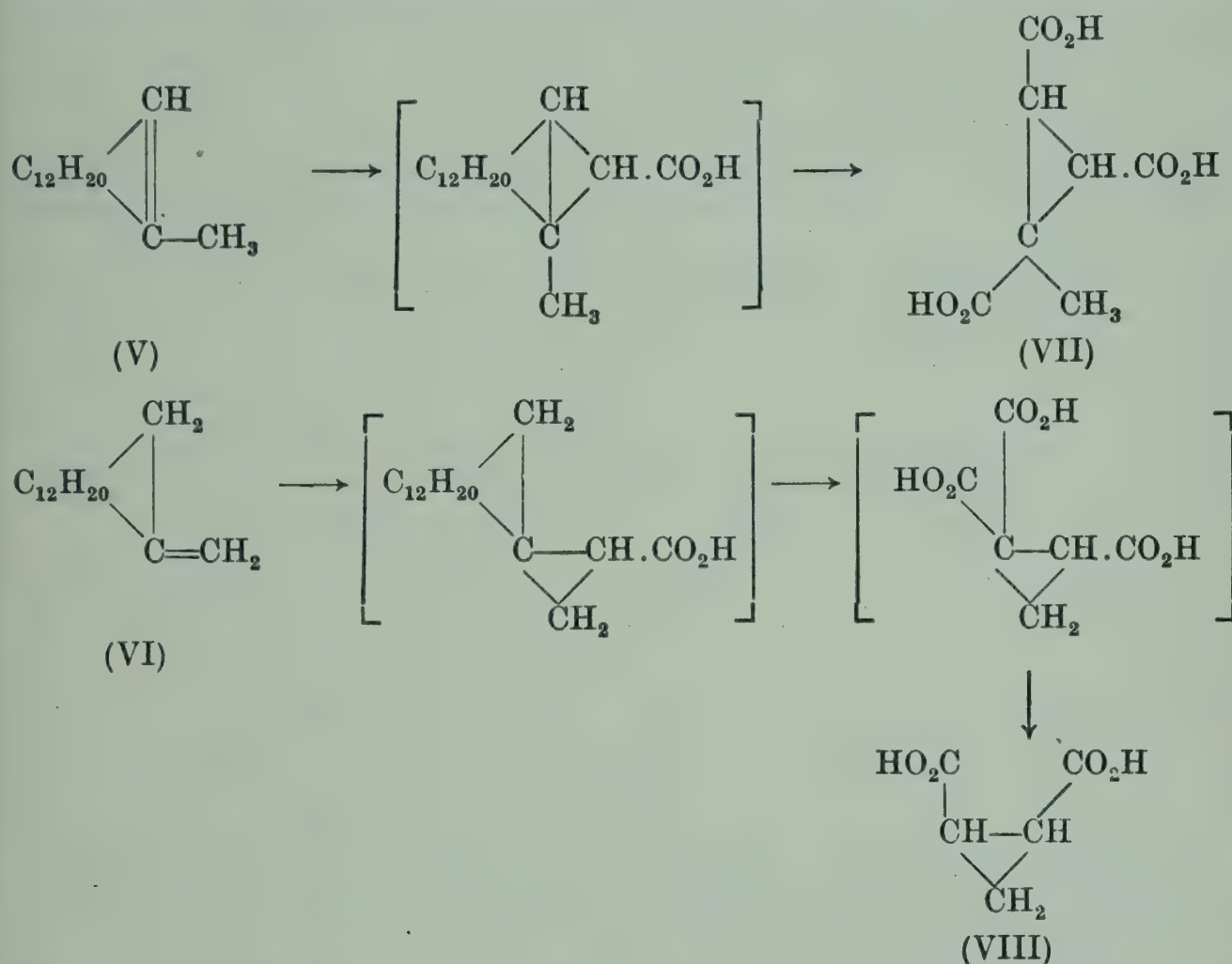
As might be expected from analogy with the α - and β -pinenes, α -cedrene, as isolated from essential oils, contains the isomeric



* Semmler and Hofmann, *Ber.* 1907, **40**, 3523; compare Treibs, *ibid.* 1935, **68**, 1041.

† Semmler and Risse, *ibid.* 1912, **45**, 355; Semmler and Mayer, *ibid.* pp. 791, 1389; Semmler and Spornitz, *ibid.* p. 1556.

hydrocarbon β -cedrene (VI). Naves, Papazian and Perrottet have shown that when α -cedrene from cedrol was condensed with ethyl diazoacetate and the resulting product oxidised with potassium permanganate only 1-methyl-cyclopropane-1:2:3-tricarboxylic acid (VII), trimethyl ester, m.p. 192° , was produced. When, however, naturally occurring cedrene was treated in a similar manner a mixture of (VII) and, after the appropriate heat treatment, cyclopropane-1:2-dicarboxylic acid (VIII), m.p. 139 –

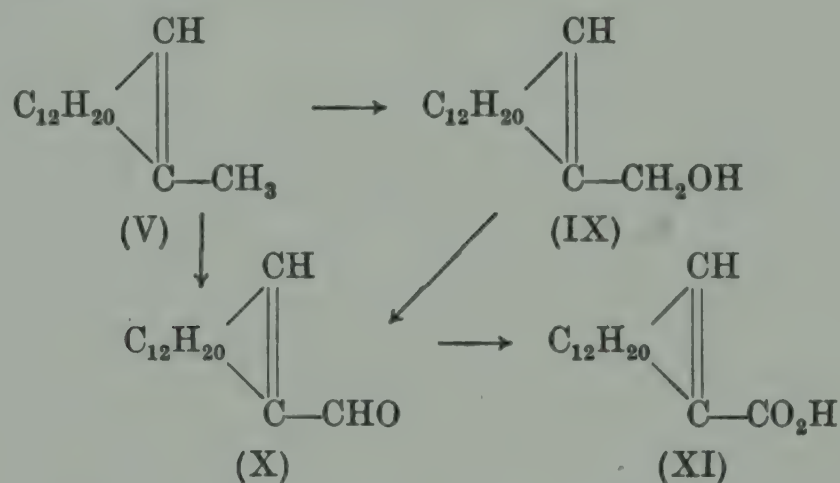


140° , anhydride, m.p. 57 – 57.5° , was obtained. Furthermore, the quantitative ozonolysis of various cedrene fractions from the natural sesquiterpene mixture has shown that the yield of formaldehyde parallels closely the deviation of the optical rotatory power from that recorded for pure α -cedrene. Pure α -cedrene, ozonised under similar conditions, gave no formaldehyde. Pure β -cedrene has not, as yet, been prepared.

The close proximity of a methyl group to the ethylenic linkage in α -cedrene, formulated as above, has been confirmed by its oxidation with selenium dioxide.* When α -cedrene was oxidised

* Treibs, *ibid.* 1937, 70, 2060; compare Naves, Papazian and Perrottet, *oc. cit.*

with this reagent in acetic anhydride solution prim.-cedrenyl acetate, $C_{17}H_{26}O_2$, b.p. $165-175^\circ/25$ mm., $d^{15^\circ} 1.032$, $n_D 1.512$, $\alpha_D -70^\circ$ was formed. This acetate was easily hydrolysed to prim.-cedrenol (see p. 170), $C_{15}H_{24}O$ (IX), b.p. $165^\circ/20$ mm., $d^{15^\circ} 1.032$, $n_D 1.517$, $\alpha_D -76.5^\circ$, which was characterised as a primary alcohol by its ease of formation of a hydrogen phthalate and by oxidation to the aldehyde cedrenal, $C_{15}H_{22}O$ (X), b.p. $163^\circ/20$ mm., $d^{20^\circ} 1.011$, $n_D 1.519$, $\alpha_D -56^\circ$, semicarbazone, m.p. 248° . The same aldehyde was obtained directly from α -cedrene by oxidation with selenium dioxide in *n*-butyl alcoholic solution. Cedrenal was smoothly oxidised by chromic acid to cedrene-carboxylic acid, $C_{15}H_{22}O_2$ (XI), m.p. 122° , methyl ester, b.p. $167-169^\circ/20$ mm., $d^{20^\circ} 1.049$, $n_D 1.503$, $\alpha_D -71^\circ$. This acid did not add bromine but was isomerised thereby to iso-cedrenecarboxylic acid (m.p. $149-150^\circ$).



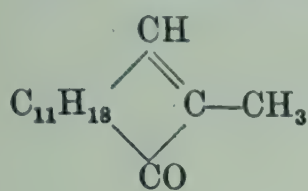
When α -cedrene is oxidised with chromic acid an $\alpha:\beta$ -unsaturated ketone called cedrenone, $C_{15}H_{22}O$ (XIII), m.p. 33° , b.p. $158-162^\circ/16$ mm., $d^{15^\circ} 1.008$, $n_D^{25^\circ} 1.5129$, $\alpha_D -78^\circ$, semicarbazone, m.p. 240.5° , is produced.* The same ketone is obtained by chromic acid oxidation of sec.-cedrenol, $C_{15}H_{24}O$ (XIV), m.p. $103.5-104^\circ$, b.p. $160^\circ/12$ mm., $[\alpha]_D -217^\circ$ (in alcohol) prepared by the catalysed oxidation of α -cedrene with moist molecular oxygen in the presence of cobalt resinate,[†] a reaction similar to the oxidation of α -pinene to verbenol (see Vol. II, p. 139), as was first recognised by Semmler and Jakubowicz.[‡] It would be anticipated, therefore, that the double bond in cedrenone would

* Rousset, *Bull. Soc. chim.* 1897 [iii], 17, 485; compare Semmler and Hofmann, *ibid.* 1907, 40, 3525; Blumann and Schulz, *Ber.* 1931, 64, 1540.

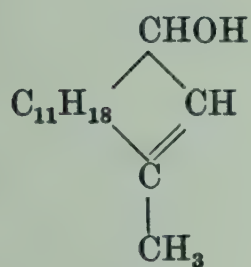
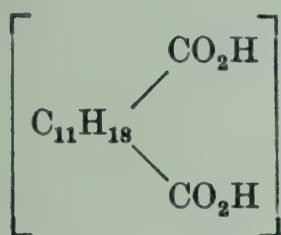
[†] Blumann, Hellriegel and Schulz, *Ber.* 1929, 62, 1698.

[‡] *Ber.* 1914, 47, 1143.

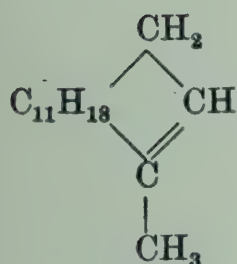
be in the same position as in α -cedrene,* and this has been proved by Ruzicka and Melsen.† When cedrenone was oxidised with ozone it afforded *norcedreneketonic acid*, $C_{14}H_{22}O_3$ (XV), m.p.



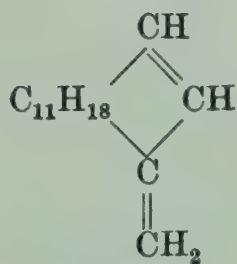
(XII)



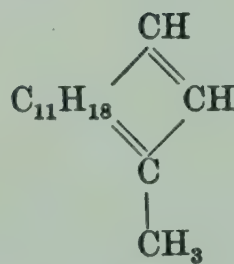
(XIV)



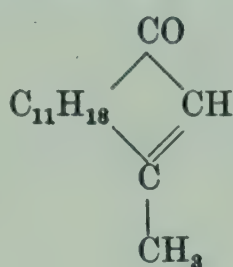
(XVII)



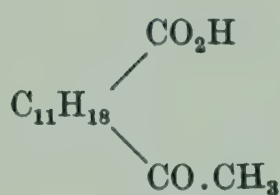
(XVIII)



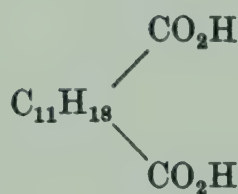
(XIX)



(XIII)



(XV)



(XVI)

113–114°, *semicarbazone*, m.p. 242–243°, which on further oxidation with sodium hypobromite gave *norcedrenedicarboxylic acid*, $C_{13}H_{20}O_4$ (XVI), m.p. 209°. This shows that cedrenone must have the formula (XIII) and not (XII) which would yield (XVI) directly without formation of the methyl ketone (XV). The partial formula for α -cedrene can be expanded, therefore, from

* Compare Blumann, Hellriegel and Schulz, *loc. cit.*; Blumann and Schulz, *loc. cit.*

† *Annalen*, 1929, 471, 54.

(V) to (XVII). Norcedrenedicarboxylic acid has also been prepared by the oxidation of *prim.*-cedrenol with potassium permanganate followed by treatment with nitric acid,* but the best method for its preparation is now stated to be by the bromination of α -cedrene with *N*-bromosuccinimide followed by oxidation with potassium permanganate and nitric acid.†

Sec.-cedrenol is dehydrated by acetic anhydride to the conjugated diene, *cedrenene*, $C_{15}H_{22}$ (XVIII), b.p. $122^{\circ}/11$ mm., $d_4^{20^{\circ}}$ 0.9432, $n_D^{20^{\circ}}$ 1.5202, $\alpha_D + 138^{\circ}$.‡ *Cedrenene* shows the expected exaltation of the molecular refraction and can be reduced by sodium and alcohol with reformation of α -cedrene and in its behaviour closely resembles verbenene (Vol. II, p. 218). *Cedrenene* forms a characteristic *dibromide*, m.p. $93-95^{\circ}$, from which it is not possible to remove both bromine atoms by the action of alkaline reagents. When *cedrenene* was oxidised by potassium permanganate, followed by nitric acid, norcedrenedicarboxylic acid was produced. This fact and the similarity already mentioned between *cedrenene* and verbenene suggest that the formula (XVIII) must represent *cedrenene* rather than the alternative formula (XIX), which would, presumably, be oxidised with loss of three in place of two carbon atoms.

Although *cedrenene* does not form an adduct with maleic anhydride, it reacts with dimethyl acetylenedicarboxylate to give a *dimethyl ester*, $C_{21}H_{28}O_4$, m.p. $132-132.5^{\circ}$, $[\alpha]_D + 83^{\circ}$ (in methanol). Since this ester can be readily reduced by catalytic hydrogenation to a saturated *ester*, $C_{21}H_{32}O_4$, m.p. $123.5-125^{\circ}$, $[\alpha]_D + 62^{\circ}$ (in methanol), it follows that it must be a normal Diels-Alder adduct. Nevertheless as *cedrenene* is not regenerated by pyrolysis its formation probably involves some molecular rearrangement.

The reactions of *cedrenene*, represented by the formula (XVIII), are best explained if the ring system containing the double bond in α -cedrene be five membered. This suggestion is in agreement with the fact that *cedrenedicarboxylic acid* cannot be cyclised under any conditions to a ketone. Thus *cedrenedicarboxylic acid*, on heating with acetic anhydride, furnished a

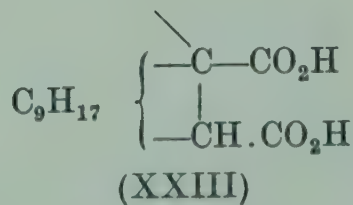
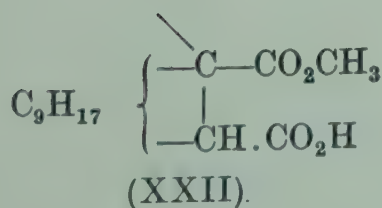
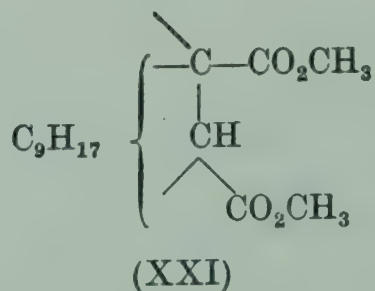
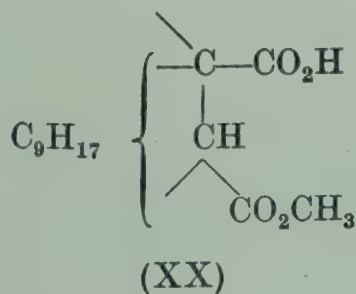
* Treibs, *loc. cit.*

† Plattner and Kläui, *Helv. Chim. Acta*, 1943, 26, 1553.

‡ Blumann and Schulz, *loc. cit.*; Ruzicka, Plattner and Kusserow, *Helv. Chim. Acta*, 1942, 25, 85.

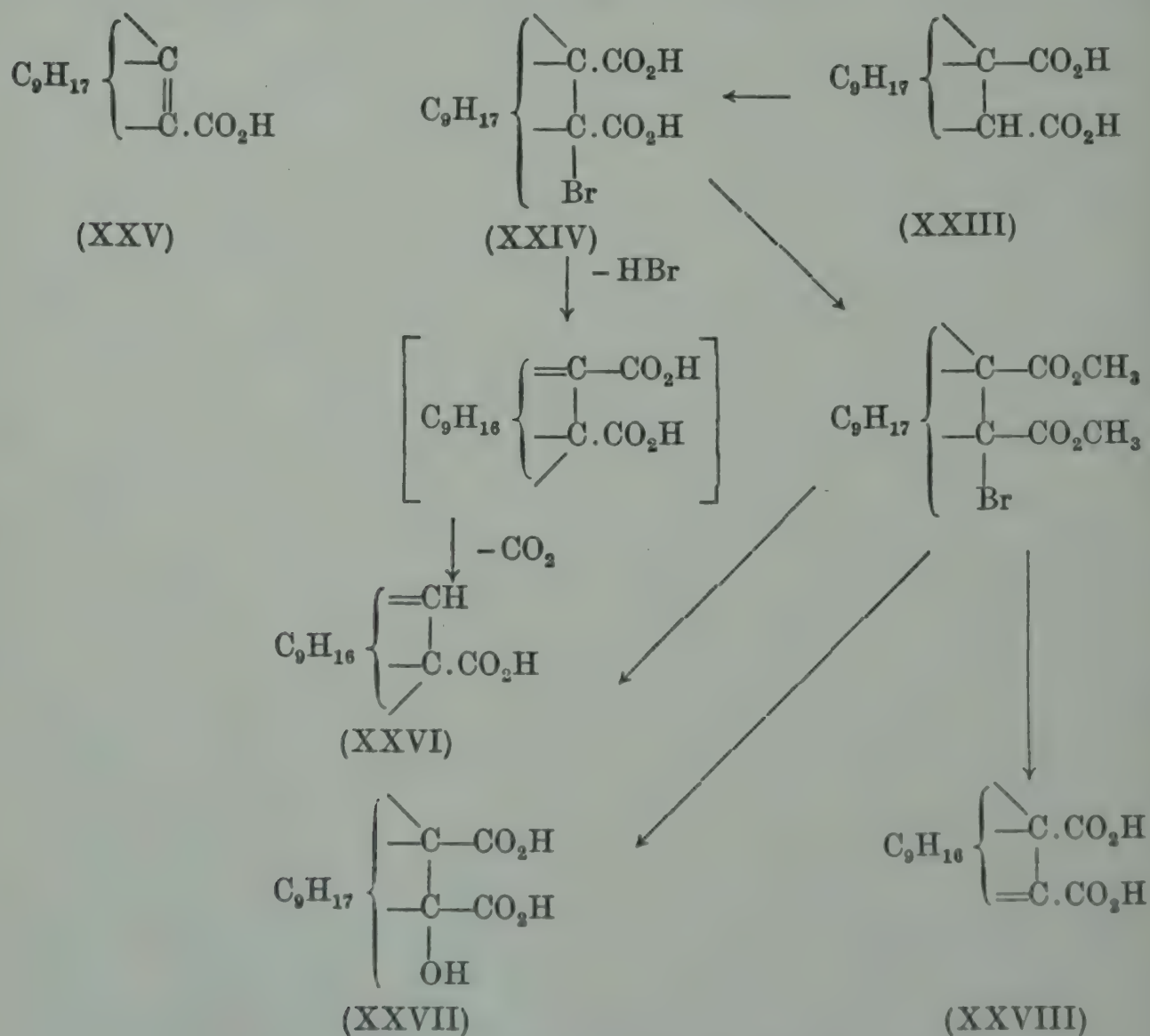
polymeric anhydride from which a probably monomeric *anhydride*, m.p. 79–82°, could be isolated by sublimation. The *anhydride*, $C_{13}H_{18}O_3$, m.p. 128–128.5°, $[\alpha]_D + 50^\circ$ (in chloroform) of norcedrenedicarboxylic acid was easily formed by similar treatment and it behaves as the derivative of a substituted succinic acid.

A careful comparison of the reactions of cedrenedicarboxylic acid and norcedrenedicarboxylic acid has enabled Ruzicka to arrive at certain conclusions regarding the structure of the latter acid. There can be no doubt that the two carboxyl groups in cedrenedicarboxylic acid are similarly situated. The acid can be readily esterified to a diethyl ester from which the acid is equally readily regenerated by hydrolysis. On bromination of the acid dibromide, a *dibromo-acid*, $C_{14}H_{20}O_4Br_2$, is formed and by the action of methyl magnesium iodide a glycol. In norcedrenedicarboxylic acid, as in camphoric acid, the two carboxyl groups have different properties. On esterification with methyl alcohol in the presence of sulphuric acid, a *hydrogen methyl ester* (XX), m.p. 98.5–99.5° is obtained, whilst the *dimethyl ester* (XXI), $d_4^{20^\circ} 1.081$, $n_D^{20^\circ} 1.4730$, $[\alpha]_D^{23^\circ} -43.5^\circ$ (in methanol), prepared with the aid of diazomethane, is only partially hydrolysed, to an isomeric *hydrogen methyl ester* (XXII), m.p. 130–131°, by alkali under conditions which cause the complete hydrolysis of diethyl cedrenedicarboxylate. On bromination norcedrenedicarboxylic acid gives a *monobromo-acid*, $C_{13}H_{19}O_4Br$, m.p. 213–214°, *dimethyl ester*, m.p. 61–62°, $[\alpha]_D -26.8^\circ$ (in methanol), whilst when dimethyl norcedrenedicarboxylate is treated with methyl magnesium iodide, a *hydroxy-ester*, $C_{16}H_{18}O_3$, b.p. 128–130°/0.3 mm., is obtained, only one ester group reacting with the Grignard reagent. Clearly norcedrenedicarboxylic acid, as indicated by



(XXIII), must contain a tertiary carboxyl group which is absent in cedrenedicarboxylic acid.

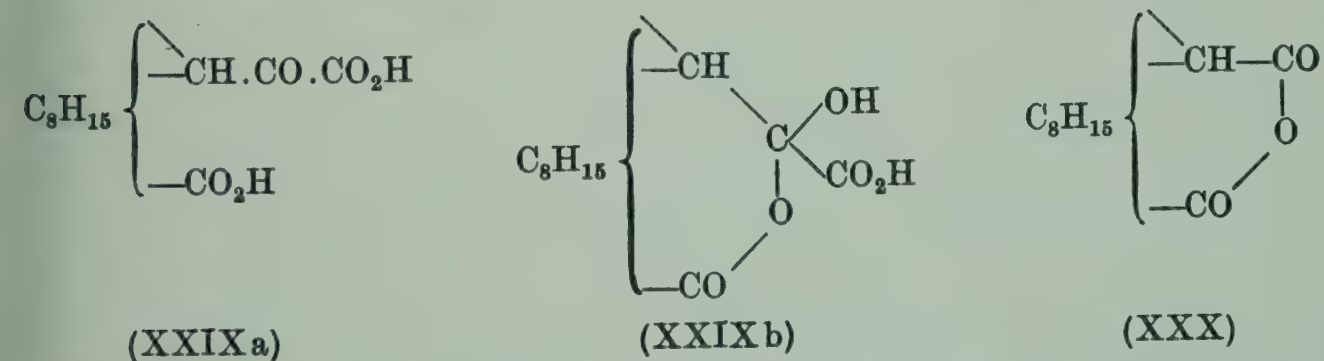
When the monobromonorcedrenedicarboxylic acid (XXIV) mentioned above was treated with alkali an unsaturated *monocarboxylic acid*, $C_{12}H_{18}O_2$, m.p. $90-91^\circ$, was formed. This acid does not show the absorption spectrum of an $\alpha:\beta$ -unsaturated acid and its methyl ester is very resistant to hydrolysis. On catalytic reduction it furnished a mixture of *dihydro-acids*, $C_{12}H_{20}O_2$, one of which melted at $60-62^\circ$. The methyl ester of this latter acid was likewise very resistant to hydrolysis. These observations suggest that the formula (XXV) cannot represent the unsaturated monocarboxylic acid and Plattner, Kusserow and Kläui* consider that it is probably formed by a rearrangement and that it is truly represented by (XXVI). This view is supported by the behaviour of the dimethyl ester of (XXIV) on alkaline hydrolysis. On prolonged treatment a mixture of



* *Helv. Chim. Acta*, 1942, 25, 1345.

(XXVI), a *hydroxy-dicarboxylic acid* (XXVII), m.p. 105° , and a *dehydronorcedrenedicarboxylic acid*, $C_{13}H_{18}O_4$ (XXVIII), m.p. $212-213^\circ$, $[\alpha]_D - 89^\circ$ (in methanol), *dimethyl ester*, $d_4^{20^\circ} 1.083$, $n_D^{20^\circ} 1.4846$, $[\alpha]_D^{23^\circ} - 70^\circ$ (in chloroform) was formed. The position of the ultra-violet absorption maximum at $230\text{ m}\mu$, $\log \epsilon = 4.2$ (in alcohol), proved the latter acid to be $\alpha:\beta$ -unsaturated, and that a rearrangement had not occurred during its formation was shown by its catalytic hydrogenation back to norcedrenedicarboxylic acid. A maleinoid type formula was excluded as dehydronorcedrenedicarboxylic acid gave only a polymeric anhydride on treatment with acetic anhydride.

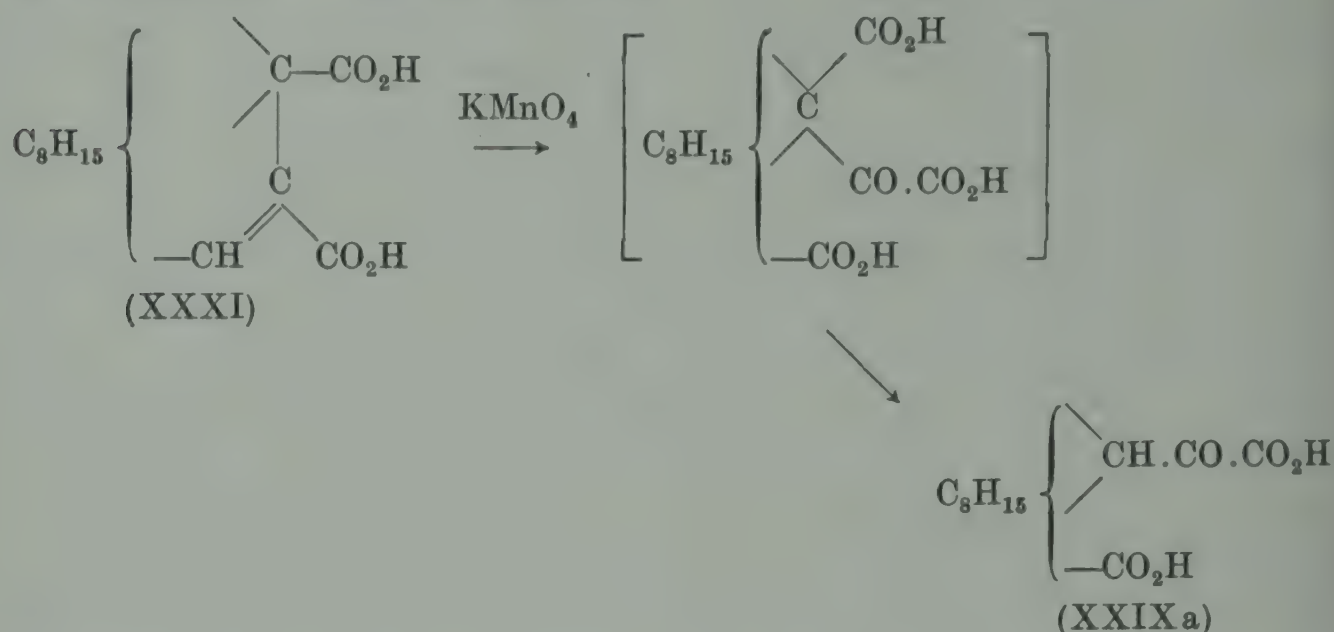
On oxidation with potassium permanganate dehydronorcedrenedicarboxylic acid (XXVIII) gave a *keto-dicarboxylic acid*, $C_{12}H_{18}O_5$ (XXIX), m.p. $142.5-143^\circ$, $[\alpha]_D - 35^\circ$ (in methanol), *p-nitrophenylhydrazone*, m.p. $182-183^\circ$, *dimethyl ester*, b.p. ca. $110^\circ/1\text{ mm.}$, $d_4^{20^\circ} 1.100$, $n_D^{20^\circ} 1.4643$, $[\alpha]_D + 21^\circ$ (in methanol) (*p-nitrophenylhydrazone*, m.p. 106°), which was further oxidised by lead tetra-acetate to a *dicarboxylic acid anhydride*, $C_{11}H_{16}O_3$ (XXX), $d_4^{20^\circ} 1.0977$, $n_D^{20^\circ} 1.4756$, $[\alpha]_D - 22.9^\circ$ (in methanol). The same anhydride was obtained by oxidation with alkaline hydrogen peroxide and its formation suggests that the formula (XXIX b) rather than (XXIX a) is more representative of the structure of the keto-dicarboxylic acid. This view is supported by the change in optical rotatory power of this latter acid when



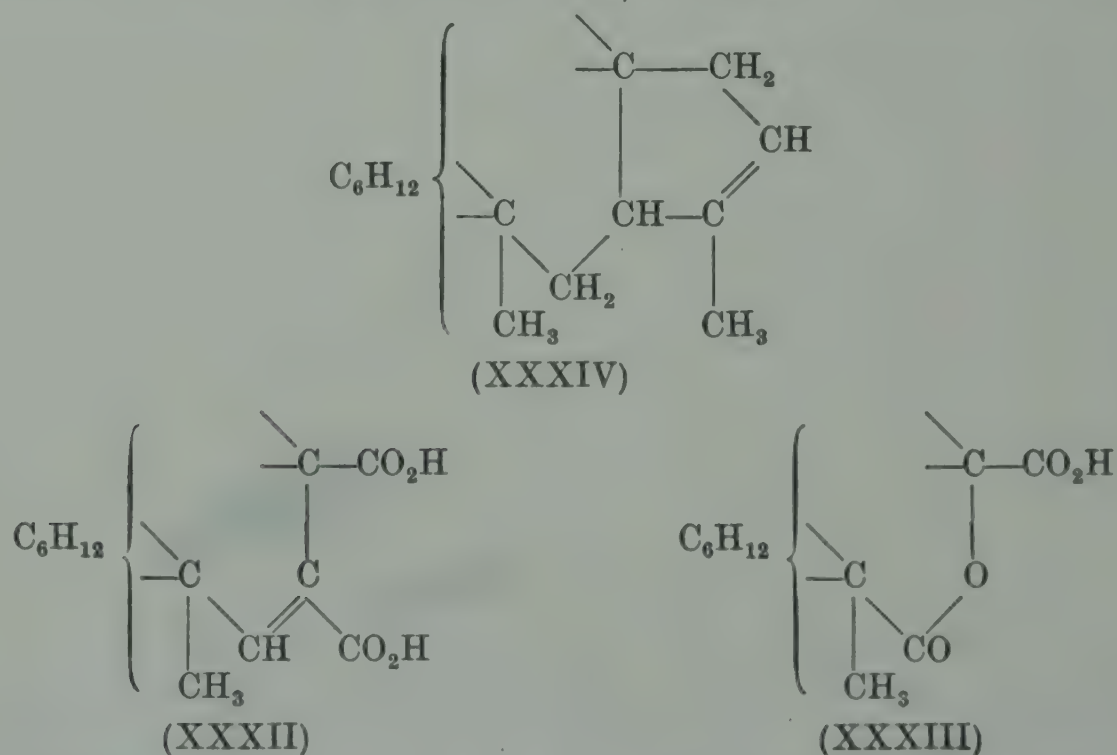
it is esterified.* The anhydride (XXX) was easily hydrolysed to the corresponding *dicarboxylic acid*, m.p. $88.5-89^\circ$, $[\alpha]_D^{14^\circ} + 15^\circ$ (in methanol), *dimethyl ester*, $d_4^{20^\circ} 1.0593$, $n_D^{20^\circ} 1.4588$, $[\alpha]_D^{23^\circ} + 26.3^\circ$ (in methanol). One of the ester groupings in the latter was sterically hindered and therefore one of the carboxyl groups in the corresponding acid is probably tertiary. The formation of the

* Compare Barton, *J.C.S.* 1946, p. 1116.

keto-dicarboxylic acid (XXIX) permits the expansion of the formula of dehydronorcedrenedicarboxylic acid from (XXVIII) to (XXXI), the oxidation to (XXIX) and to (XXX) proceeding in accordance with the scheme:



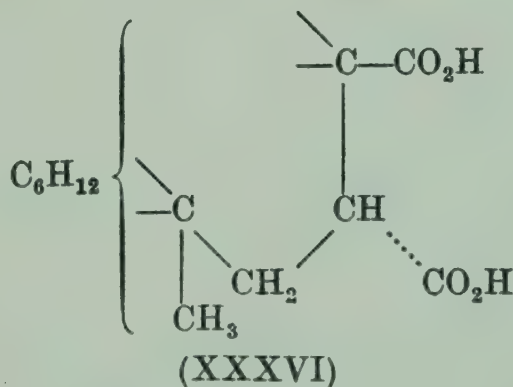
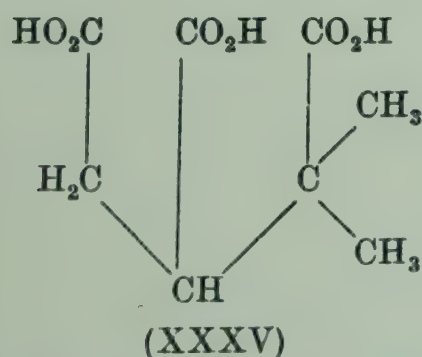
Further, if one of the carboxyls in the acid corresponding to (XXX) is to be tertiary then the formula (XXXI) must be replaced by (XXXII). Support for this view was furnished by the fact that the anhydride (XXX) could only be monobrominated and the resulting bromo compound gave a *lactone carboxylic*



acid (possibly (XXXIII)), $\text{C}_{11}\text{H}_{16}\text{O}_4$, m.p. 187° , on refluxing with methanol. The formula for α -cedrene can, therefore, now be expanded, from (XVII) to (XXXIV).

Treibs* has examined the oxidation of the acid (XXVI) (p. 82) with potassium permanganate. A crude dihydroxy-acid was produced that could not be purified, but which could be degraded further by oxidation with lead tetra-acetate to a mixture of a doubly *unsaturated* acid, $C_{12}H_{16}O_2$, m.p. 146–147° and a *ketonic acid*, $C_{12}H_{16}O_3$, *semicarbazone*, m.p. 267°. It is not possible at present to formulate these products nor the somewhat similar products obtained by Plattner, Kusserow and Kläui† by the oxidation of (XXVI) with perbenzoic acid followed by hydrolysis of the mixed oxides thus formed.

An important degradational fragment of the cedrene molecule was first obtained by Treibs‡ by vigorous oxidation of cedrene with potassium permanganate followed by nitric acid. This fragment was at first identified as camphoronic acid, but a more thorough investigation has shown that it is actually $\alpha:\alpha$ -dimethyl-tricarballic acid (XXXV).§ This acid can also be prepared by a similar degradation of *prim.*-cedrenol or by nitric acid oxidation of norcedrenedicarboxylic acid. As by-products in these oxidations the formation of acetic, oxalic, dimethylmalonic and *as*-dimethylsuccinic acids has frequently been reported. Treibs has also claimed that an *isonorcedrenedicarboxylic acid*, m.p. 130°, is formed under these conditions. It would be expected that this acid would be a stereoisomer of norcedrenedicarboxylic acid, but Plattner and Kläui have shown that *trans*-norcedrenedicarboxylic acid (XXXVI), which was obtained as a by-product during an attempt to prepare dehydronorcedrenedicarboxylic acid, has m.p. 222.5–223°, $[\alpha]_D - 53.3^\circ$ (in chloroform), and reverts to the usual *cis*-norcedrenedicarboxylic acid anhydride on treatment with acetic anhydride. The structure of the acid described by



* Ber. 1943, 76, 160.

‡ Ber. 1935, 68, 1041.

§ Treibs, *ibid.* 1943, 76, 160; Plattner and Kläui, *Helv. Chim. Acta*, 1943, 26, 1553.

† Loc. cit.

Treibs is, therefore, uncertain, but it is clear that the five-membered ring of cedrene must be bound in the *cis* position to the residual bicyclic portion of the molecule. It was mentioned above (p. 81) that when dimethyl norcedrenedicarboxylate is treated with methyl magnesium iodide a hydroxy-ester, $C_{16}H_{18}O_3$, is formed. This hydroxy-ester was oxidised with chromic acid by Ruzicka and Melsen* with formation of a dicarboxylic acid, *cedrenecamphoric acid*, $C_{10}H_{16}O_4$, *dimethyl ester*, b.p. $166^\circ/12$ mm., $d_4^{20^\circ}$ 1.102, $n_D^{20^\circ}$ 1.472. It has recently been suggested by Plattner, Kusserow and Kläui that this acid may be inhomogeneous, and its importance in cedrene chemistry should not be overestimated, therefore, until it has been thoroughly re-examined.

The experiments of Ruzicka and Melsen have shown that the formulae for cedrene of Semmler† and of Deussen‡ cannot be correct. Likewise the characterisation of $\alpha:\alpha$ -dimethyltricarballic acid as a degradation product of cedrene excludes the formulae of Short§ and of Robinson and Walker,|| since they were both based on Treibs' supposed isolation of camphoronic acid. The formula of Naves, Papazian and Perrottet¶ is similarly unsatisfactory and cannot explain many other well-established properties of cedrene and its derivatives. It must be concluded that no suitable formula has, as yet, been proposed.

Cedrene can be readily reduced catalytically to give *dihydrocedrene*, b.p. $110^\circ/4$ mm., $d_4^{20^\circ}$ 0.9262, $n_D^{20^\circ}$ 1.4915, $[\alpha]_D -6.16^\circ$ (compare p. 87), which is isomerised by aluminium chloride to *anisodihydrocedrene*, b.p. $90-92^\circ/1.6$ mm., $d_4^{20^\circ}$ 0.9028, $n_D^{20^\circ}$ 1.4831, $\alpha_D -0.52^\circ$. When cedrene is oxidised with manganese dioxide and sulphuric acid phthalic acid is obtained.** Gibson, Robertson and Sword†† have shown that the hydrocarbon reacts with chromyl chloride to give an *addition compound*, $C_{15}H_{24}$, $2\frac{1}{2}CrO_2Cl_2$, which is decomposed by water yielding a *substance*, $C_{15}H_{24}O$, b.p. $93^\circ/0.015$ mm., $n_D^{15^\circ}$ 1.5462, which is apparently either an aldehyde or a ketone. By the action of mercuric acetate in acetic acid solution an alcohol is formed, possibly identical with pseudo-cedrol (p. 172).**

* *Annalen*, 1929, 471, 54.

† *J. pr. Chem.* 1927 [ii], 117, 297.

‡ *Chem. and Ind.* 1935, 13, 874.

§ *Helv. Chim. Acta*, 1943, 26, 302.

†† *J.C.S.* 1926, p. 166.

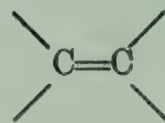
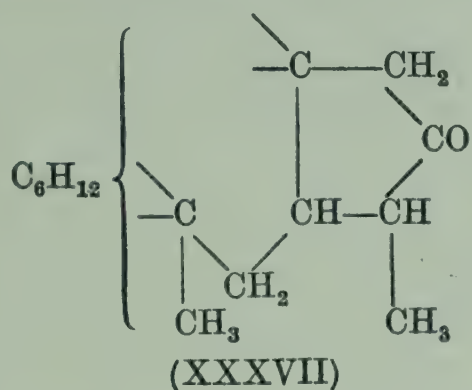
† *Ber.* 1914, 47, 2558.

|| *Ibid.* 1935, 13, 906, 946.

** Deussen, *loc. cit.*

†† Bell, *ibid.* 1930, 1908.

Cedrene furnishes a ketone, *cedranone*, $C_{15}H_{24}O$ (XXXVII), b.p. $134^{\circ}/4$ mm., $d_4^{20^{\circ}}$ 1.0024, $n_D^{20^{\circ}}$ 1.4998, $\alpha_D -84.7^{\circ}$, *oxime*, m.p. $103.5-104^{\circ}$, $[\alpha]_D -78.59^{\circ}$ (in chloroform) on treatment with hydrogen peroxide. The same ketone is obtained by the dehydration of cedrene glycol (I) (p. 76) with sulphuric acid.*



(XXXVIII)

When cedrene is treated with cold concentrated sulphuric acid complex monomeric and polymeric products are formed. Among the former a *dehydrocedrene*, $C_{15}H_{22}$, b.p. $88^{\circ}/1.8$ mm., $d_4^{20^{\circ}}$ 0.9438, $n_D^{20^{\circ}}$ 1.5222, $\alpha_D +6.20^{\circ}$ and an *isomer* of cedrene, $C_{15}H_{24}$, b.p. $93^{\circ}/2.3$ mm., $d_4^{20^{\circ}}$ 0.9231, $n_D^{20^{\circ}}$ 1.4928 have been recognised.[†] Dehydrocedrene is soluble in concentrated sulphuric acid and can be catalytically hydrogenated, but with uptake of only one molecular proportion of hydrogen, to give a *dihydrodehydrocedrene*, $C_{15}H_{24}$, b.p. $84^{\circ}/1.3$ mm., $d_4^{20^{\circ}}$ 0.9280, $n_D^{20^{\circ}}$ 1.4966, $\alpha_D -2.30^{\circ}$, which would be better termed *pseudocedrene*. Both this latter compound and the isomer of cedrene mentioned above are completely resistant to catalytic reduction and therefore probably have the double bond in a bridge position, as illustrated in (XXXVIII). The formation of these compounds must involve extensive rearrangement of the cedrene molecule.

Cedrene is also isomerised when it is digested for some hours with formic acid[‡] or when it is heated to 330° under pressure.[§] In neither case have the products which are formed been identified. However, if cedrene vapour is led over a nickel catalyst at $420-450^{\circ}$, a good yield of *p*-cymene (up to 30 per cent.) can be obtained.^{||}

* Naves, Papazian and Perrottet, *Helv. Chim. Acta*, 1943, **26**, 302; compare Treibs, *Ber.* 1935, **68**, 1041.

† Naves, Papazian and Perrottet, *Helv. Chim. Acta*, 1943, **26**, 302.

‡ Robertson, Kerr and Henderson, *J.C.S.* 1925, **127**, 1946.

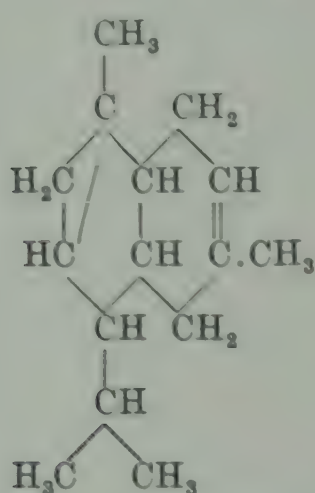
§ Semmler and Jakubowicz, *Ber.* 1914, **47**, 2257.

|| Treibs, *ibid.* 1935, **68**, 1041.

Cedrene is stated to yield a *nitrosochloride*, m.p. 100–102°, but this substance has not been fully investigated.*

The conversion of cedrene to a doubly unsaturated *hydrocarbon*, $C_{12}H_{18}$, b.p. 85–87°/10 mm., $d_4^{21^\circ}$ 0.9229, $n_D^{21^\circ}$ 1.4983, has been reported by Ruzicka and Jutassy.† Cedrene was oxidised to cedrenedicarboxylic acid, which was degraded by the hydrazoic acid method to the corresponding *diamine*, $C_{12}H_{24}N_2$, and this by the Hofmann procedure was converted to the above-mentioned hydrocarbon.

COPAENE



African oil of copaiba, which is obtained from *Oxystigma Mannii* Harms, was observed by Schimmel and Co.‡ to contain a laevo-rotatory hydrocarbon, $C_{15}H_{24}$, which, although it differed considerably from cadinene in its properties, gave *l*-cadinene dihydrochloride by the action of hydrogen chloride. Later the same hydrocarbon was separated by Henderson, M'Nab and Robertson§ from oil of supa, obtained from the tree *Sindora Wallichii* Benth.

The hydrocarbon, to which the name *copaene* has been given, is a colourless viscid oil, b.p. 114–114.5°/10 mm., $d_4^{25^\circ}$ 0.955, $n_D^{25^\circ}$ 1.488 to 1.4895, $[\alpha]_D^{13.5^\circ}$ -0.44° to -1.2° .|| The reactions of the hydrocarbon were first investigated by Semmler and Stenzel,¶ who showed it to be a tricyclic hydrocarbon containing one

* Schimmel's Report, 1904, II, 20; Chapman and Burgess, *Proc. C.S.* 1896, p. 140.

† *Helv. Chim. Acta*, 1936, 19, 322.

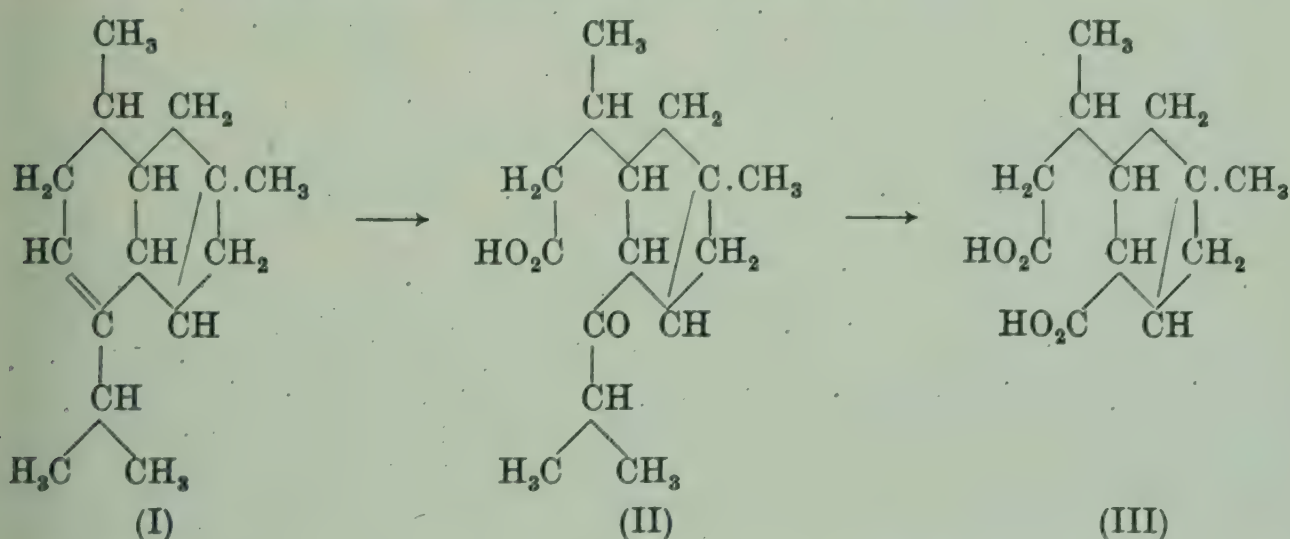
‡ Schimmel's Report, 1914, April, p. 48.

§ *J.C.S.* 1926, p. 3077.

|| Briggs and Taylor, *ibid.* 1947, p. 1338; compare Downes, Gill and Lions, *Australian J. Sci.* 1948, 10, 147; Briggs, Gill, Lions and Taylor, *J.C.S.* 1949, p. 1098.

¶ *Ber.* 1914, 47, 2555.

tained the group $\begin{array}{c} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{array} \rangle \text{CH} \cdot \text{CO}—$. They suggested that copaeene might be represented by the structure (I) when the keto-acid would be (II) and the dicarboxylic acid (III).



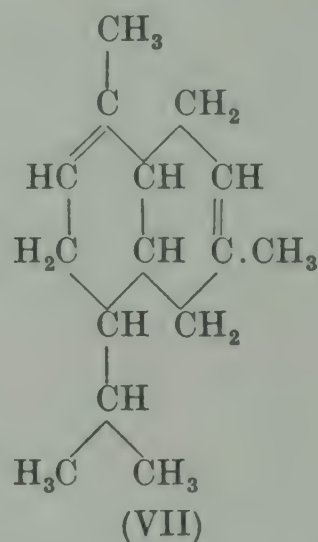
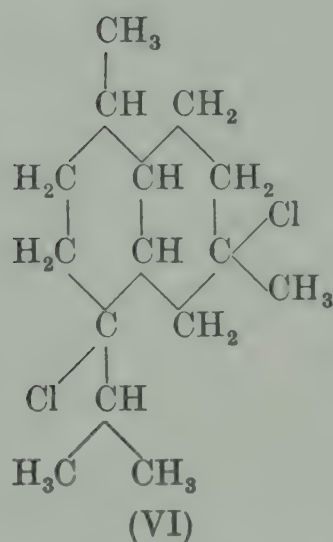
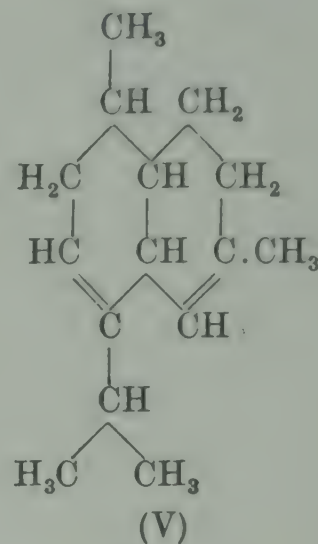
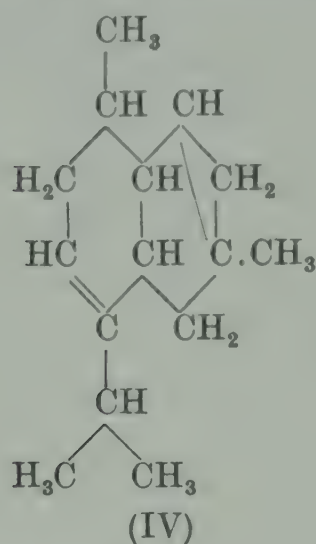
Since, however, copaene on treatment with hydrogen chloride yields cadinene dihydrochloride it must contain the same carbon skeleton as cadinene and in 1926 Henderson, M'Nab and Robertson[†] replaced (III) by (IV), cadinene dihydrochloride on the then accepted cadinene formula (V) (compare p. 28) being represented by (VI). As has been described on p. 27, Campbell and Soffer[‡] have now shown that cadinene must be represented

* The copaene used by Semmler and Stenzel had $[\alpha]_D -13.21^\circ$; they record also a somewhat higher boiling-point $119-120^\circ/10$ mm.

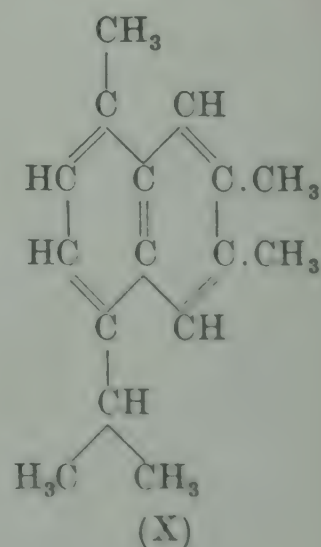
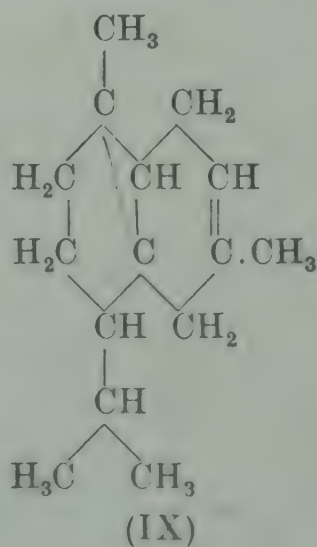
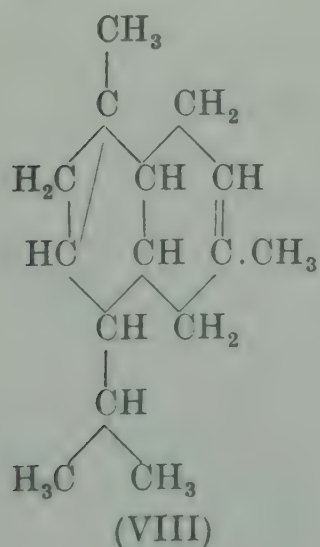
† *Loc. cit.*

* *J. Amer. C.S.* 1942, 64, 417.

by (VII) and it follows therefore that neither (I) nor (IV) can be correct representations of copaene.

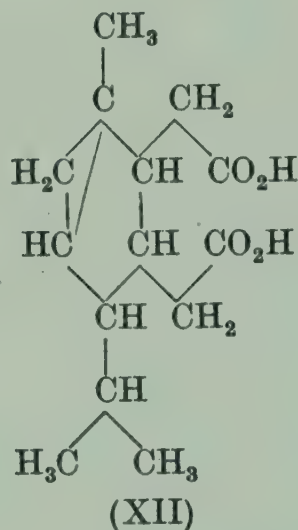
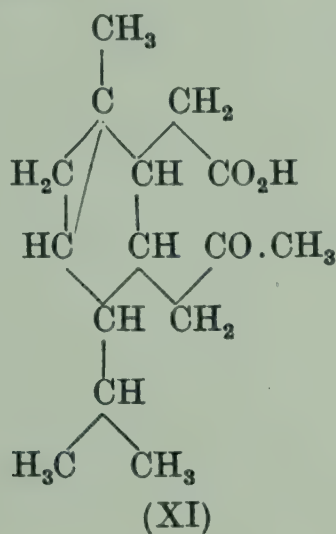


Following the method adopted by Campbell and Soffer for the determination of the structure of cadinene, Briggs and Taylor* have treated copaene with perbenzoic acid. The resulting oxide, which distilled over a somewhat wide range due possibly to ring fission or partial isomerisation to the ketone, was allowed to

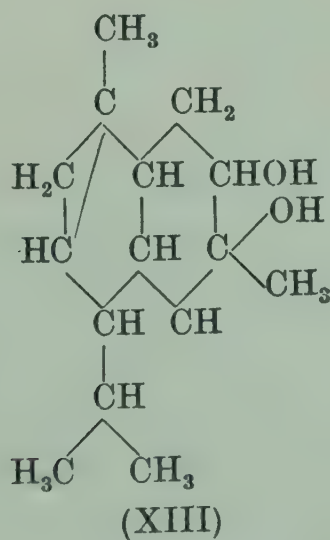


* *Loc. cit.*

react with an excess of methyl magnesium iodide and the carbinol so obtained was dehydrated with formic acid and then dehydrogenated with selenium. The aromatic hydrocarbon prepared in this manner was identified as 1:6:7-*trimethyl-4-isopropyl naphthalene* (X). Copaene must therefore be represented by either (VIII) or (IX). Of these two formulae (VIII) is preferable, since (IX), on dehydrogenation with selenium like ledol (see p. 172), might be expected to give an azulene in addition to cadalene, which is, however, not the case. If (VIII) correctly represents copaene, then Semmler and Stenzel's keto-acid must be (XI), and their dibasic acid (XII) having the formula $C_{14}H_{22}O_4$ and not $C_{12}H_{18}O_4$. A reinvestigation of these oxidation products is desirable.



As a further product of the oxidation of copaene with potassium permanganate Semmler and Stenzel obtained a *glycol*, $C_{15}H_{26}O_2$ (XIII), b.p. 178–185°/17 mm., $d^{17^\circ} 1.039$, $n_D 1.5026$, $[\alpha]_D + 13^\circ$.



LONGIFOLENE

The tricyclic sesquiterpene, *longifolene*, $C_{15}H_{24}$, b.p. 254–256°/706 mm., 150–151°/36 mm., d_{30}^{30} 0.9284, n_D^{30} 1.4950, $[\alpha]_D + 42.73^\circ$, has been shown by Simonsen* to occur in the essential oils obtained from the oleo-resins of *Pinus longifolia*, *P. Khasya* and *P. Merkusii*.† It can be identified by the preparation of the *hydrochloride*, m.p. 59–60°, $[\alpha]_D + 7.1^\circ$, the *hydrobromide*, m.p. 69–70° and the *hydriodide*, m.p. 71°.

The constitution of this hydrocarbon has not been proved with certainty, but its reactions have been studied in considerable detail by Simonsen,‡ and by Bradfield, Francis and Simonsen.§ When it is oxidised with chromic acid in acetic acid solution, it yields, in addition to a diketone which will be referred to later, a monobasic acid, *longifolic acid*, $C_{14}H_{22}O_2$, m.p. 152–153°, *methyl ester*, b.p. 170–173°/14 mm., which was readily isomerised by treatment with mineral acid to *isolongifolic acid*, m.p. 136°, $[\alpha]_{5461} - 12.7^\circ$ (in alcohol), *methyl ester*, m.p. 54–55°, $[\alpha]_{5461} + 5.94^\circ$ (in methyl alcohol), *anilide*, m.p. 197°. The same acid can be prepared very much more conveniently by direct oxidation of the sesquiterpene with potassium dichromate and sulphuric acid. On reduction with sodium in alcoholic solution, *methyl isolongifolate* gives the alcohol, *isolongifolol*, $C_{14}H_{24}O$, m.p. 112–114°, *phenylurethane*, m.p. 91–92°, which can be oxidised to the aldehyde, *isolongifaldehyde*, b.p. 170°/35 mm., *semicarbazone*, m.p. 210°. The formation of these saturated acids by the oxidation of the sesquiterpene can best be explained by the presence of the vinyl grouping. This assumption has been confirmed by ozonolysis, when formaldehyde and a saturated acid, α -longifolic acid, $C_{14}H_{22}O_2$, m.p.s 140–142° and 121–122°, $[\alpha]_{5461} - 31^\circ$ (in ethyl alcohol) were produced. The relationship between α -longifolic acid and longifolic and isolongifolic acids has not been determined with certainty, but they are all possibly stereoisomers involving two centres of asymmetry. All these acids are esterified with difficulty and similarly the hydrolysis of their esters is sterically repressed. They are doubtless therefore

* *J.C.S.* 1920, 117, 578; *Ind. For. Rec.* 1922, 9, 113, 1923, 10, 52.

† It is also present in the oil from *Pinus maritima* (Dupont, Dulou and Naffa, *Bull. Soc. chim.* 1948 [v], 15, 990).

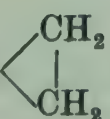
‡ *J.C.S.* 1923, 123, 2642.

§ *Ibid.* 1934, p. 188.

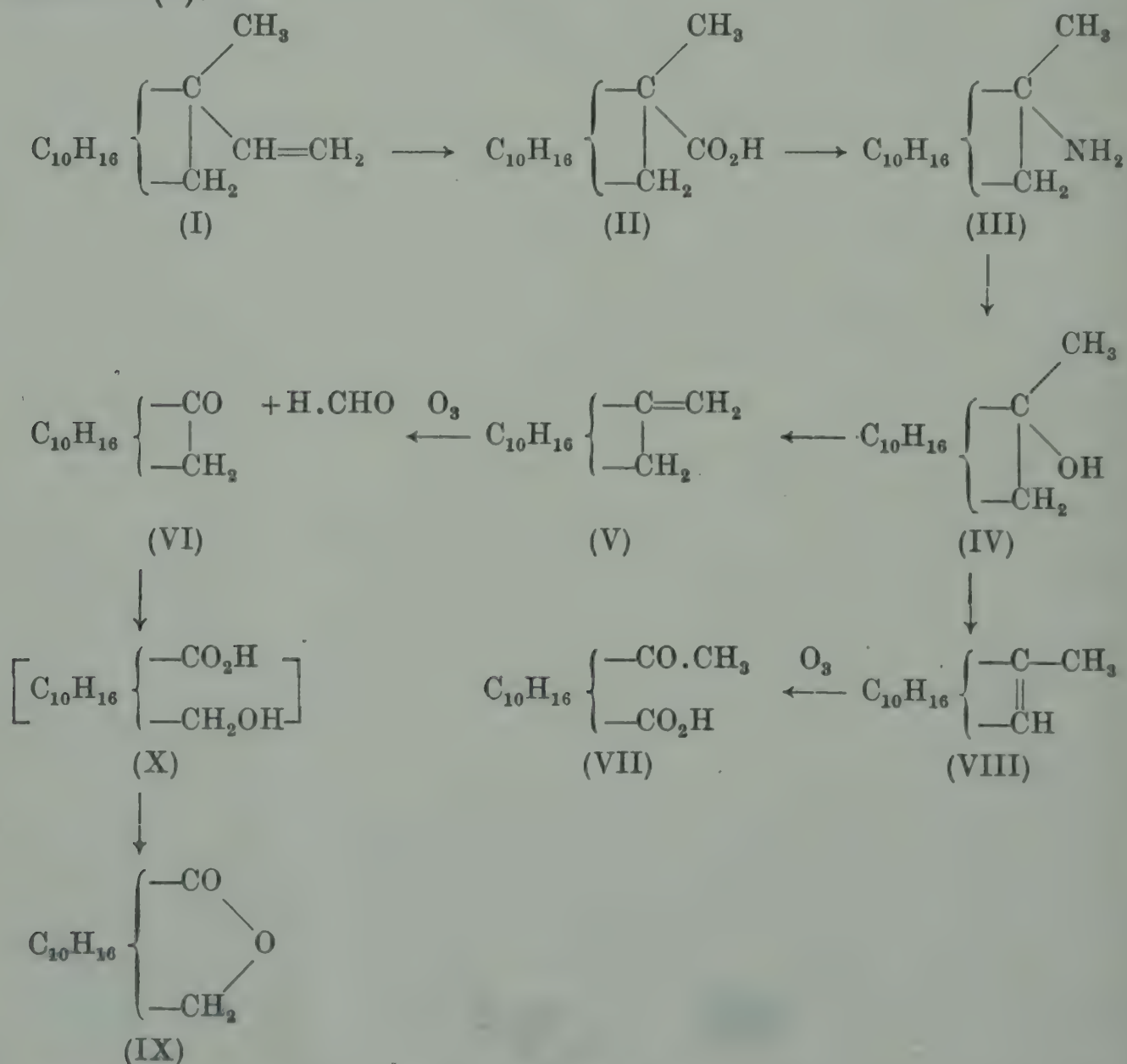
tertiary carboxylic acids, which conclusion is supported by the fact that they cannot be brominated.

Bradfield, Francis and Simonsen* have converted a mixture of longifolic and isolongifolic acids to the corresponding mixed amides and thence to the mixed urethanes from which a crystalline urethane, $C_{15}H_{25}O_2N$, m.p. $76-77^\circ$, $[\alpha]_{5461} - 11.1^\circ$ (in methyl alcohol) could be isolated. On hydrolysis with sodium amyloxide the mixed urethanes gave a mixture of 1-amino-1-methyl-longifanes, $C_{13}H_{23}N$, b.p. $150^\circ/18$ mm., $[\alpha]_{5461} - 35.3^\circ$ (in alcohol),† the presence of the methyl group in these compounds following from oxidation experiments described below. The mixture of bases was characterised by the formation of a hydrochloride, m.p. $280-282^\circ$, decomp., a nitrite, m.p. 132° decomp., two acetyl derivatives, $C_{15}H_{25}ON$, m.p. $191-192^\circ$, $[\alpha]_{5461} - 56.4^\circ$ (in alcohol), and m.p. $163-165^\circ$, a 3:5-dinitrobenzoate, m.p. $199-200^\circ$, $[\alpha]_{5461} - 12.2^\circ$ (in chloroform), and two methiodides, $C_{16}H_{30}NI$, m.p. $258-259^\circ$ and m.p. 184° decomp. The mixture of 1-amino-1-methyl-longifanes was degraded by treatment with nitrous acid in the presence of phosphoric acid to a mixture of alcohols and hydrocarbons which, without purification, was dehydrated by heating with potassium bisulphate to a mixture of saturated and unsaturated hydrocarbons, $C_{13}H_{20}$, b.p. $124^\circ/20$ mm., $d_{25}^{25^\circ} 0.95$, $n_D^{25^\circ} 1.4995$, $[\alpha]_{5461} + 6.04^\circ$ (in acetone), shown by peracid titration to consist of about equal amounts of tricyclic and tetracyclic substances. Oxidation of these mixed hydrocarbons with potassium permanganate furnished a dibasic acid, $C_{13}H_{20}O_4$, m.p. $235-236^\circ$, which formed a liquid anhydride on treatment with acetyl chloride hydrolysed back to the same dicarboxylic acid, and a lactone, $C_{12}H_{18}O_2$, m.p. 190° . Ozonolysis gave formaldehyde and a ketone, $C_{12}H_{18}O$, semicarbazone, m.p. $208-209^\circ$, containing a methylene group adjacent to the carbonyl grouping, since it afforded a liquid hydroxymethylene derivative, semicarbazone, m.p. 199° . The saturated tetracyclic hydrocarbon, 1-methyldehydrolongifane, b.p. $125-127^\circ/25$ mm., $d_{25}^{25^\circ} 0.9514$, $n_D^{24^\circ} 1.4967$, $[\alpha]_{5461} + 18.8^\circ$ (in ethyl acetate) was recovered un-

* Loc. cit.

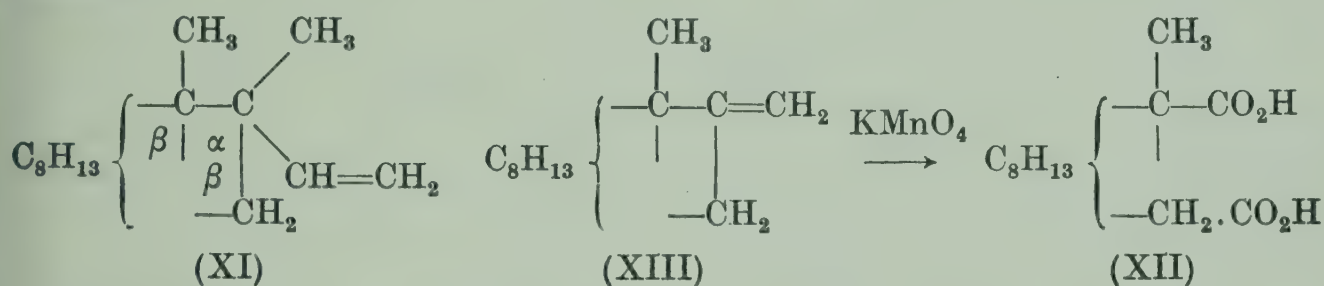
† The tricyclic nucleus $C_{10}H_{16}$  present in longifolene has been designated longifane.

attacked after the ozonolysis. By treatment with hydrogen chloride this saturated hydrocarbon gave a liquid monohydrochloride, thus suggesting the presence of a *cyclopropane* ring, and this view was supported by the observed exaltation of the molecular refraction ($[R_L]_D = 54.11$; calc. for $C_{13}H_{20}$, 53.60). The series of reactions described above can most readily be explained by the following scheme, where (I) represents longifolene, (II) the mixed longifolic acids, (III) the mixed 1-amino-1-methyl-longifanes, (IV) the corresponding alcohols, and (V) the corresponding unsaturated hydrocarbon, giving rise to the $C_{12}H_{18}O$ ketone (VI) and formaldehyde on ozonolysis, and thus proving that longifolene is 1-methyl-1-vinyl-longifane as already formulated in (I).



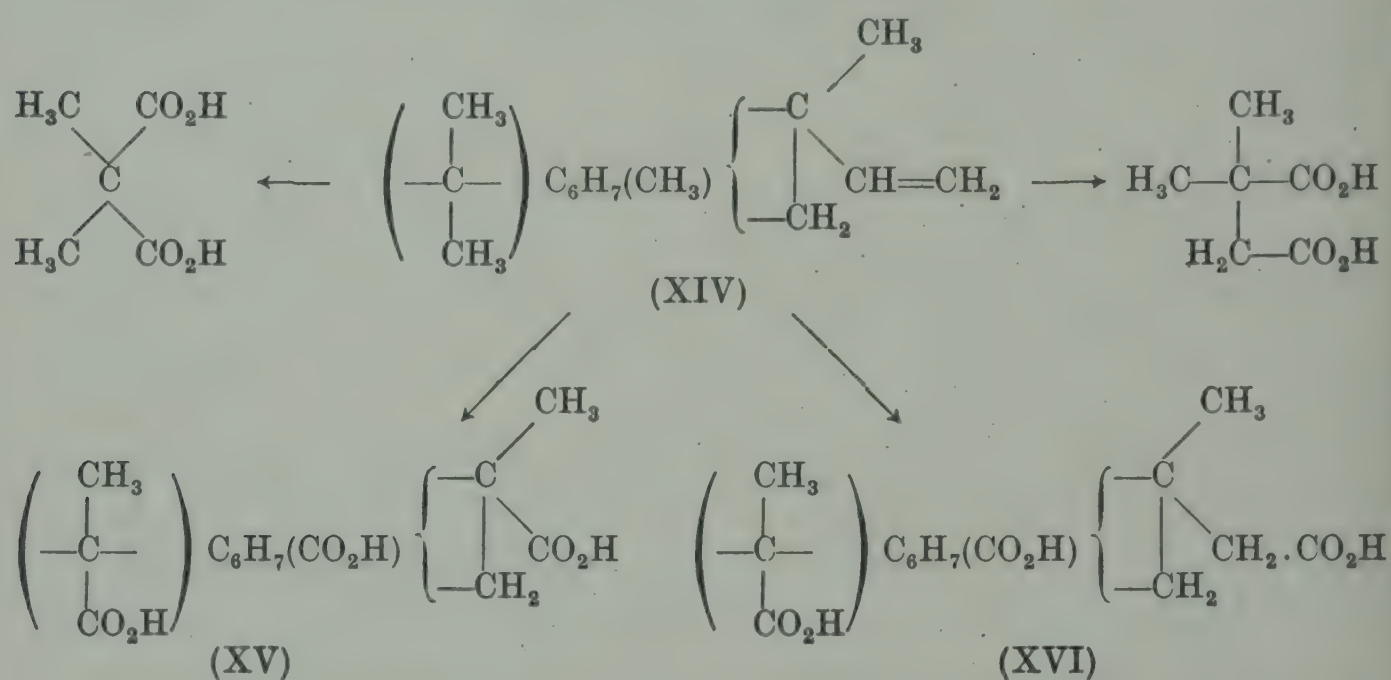
The acid fraction of the mixed hydrocarbon ozonolysis described above, although not obtained in a state of purity, gave reactions for a methyl ketone, probably (VII), so that the olefinic

isomer (VIII) of the hydrocarbon (V) was probably present in the original mixture, as might be expected. The lactone, $C_{12}H_{18}O_2$, obtained by permanganate oxidation, was formulated as (IX), being formed *via* the intermediate hydroxy-acid (X) from the ketone (VI). The dicarboxylic acid, $C_{13}H_{20}O_4$, also formed by the permanganate oxidation, was considered to be produced in the same way that camphenic acid is obtained by the oxidation of camphene (see Vol. II, p. 284), so that one of the β -carbon atoms in longifolene is probably not attached to a hydrogen atom. This suggested that the formula of longifolene could be expanded from (I) to (XI), the dibasic acid $C_{13}H_{20}O_4$ now being represented by (XII) and the hydrocarbon (V) by (XIII).



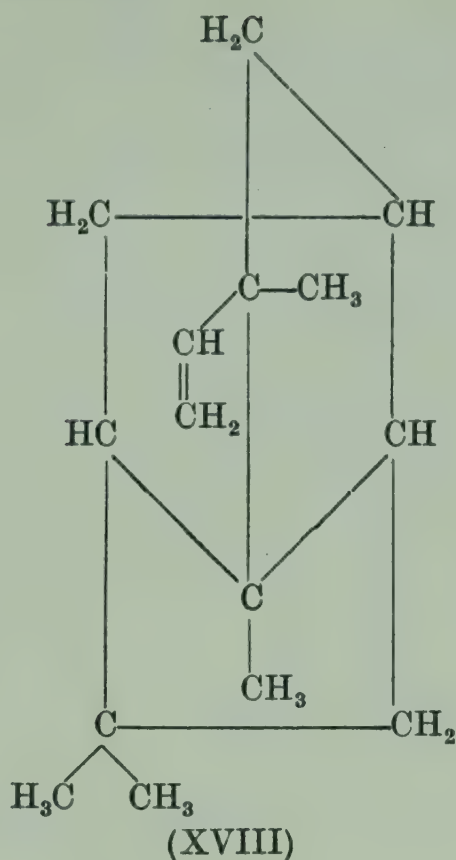
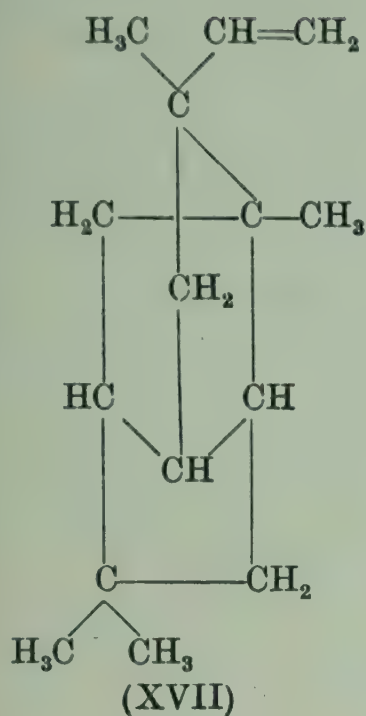
Further insight into the structure of longifolene was obtained by a study of its oxidation with manganese dioxide and sulphuric acid, when *trimellitic acid* was produced, and with nitric acid, when an extremely complex mixture of acids was obtained. Among these were *dimethylmalonic acid*, *as-dimethylsuccinic acid*, a *tribasic acid*, $C_{14}H_{18}O_6$, m.p. 283–285° decomp., *trimethyl ester*, m.p. 73–74°, $[\alpha]_{5461} + 42.2^\circ$ (in ethyl acetate), a second *tribasic acid*, $C_{15}H_{20}O_6$, m.p. 222–224° decomp., $[\alpha]_{5461} + 52.81^\circ$ (in ethyl alcohol), and a *dibasic acid*, $C_{11}H_{18}O_4$, m.p. 183–185°. The isolation of *as-dimethylsuccinic acid*, which can also be obtained by direct oxidation of longifolene with potassium permanganate, and of dimethylmalonic acid proves the presence of a *gem*.-dimethyl group in the sesquiterpene. The first tribasic acid, which was formed in the largest quantity, was extremely stable and all three of its carboxyl groups were apparently attached to quaternary carbon atoms, for the same reasons that the longifolic acids (see above) were regarded as thus constituted. Its formation from longifolene can be readily explained if its three carboxyl groups are formed by oxidation of (i) the vinyl group and (ii) two methyl groups not attached to the same carbon

atom. The methyl group attached to the same carbon atom as the vinyl group cannot be involved, and, since the tribasic acid is not a substituted malonic acid, only one of the methyl groups of the *gem*.-dimethyl group is concerned in its formation. This necessitates the presence in the hydrocarbon of a further methyl group and enables the formula of longifolene to be expanded from (X) to (XIV), so that the tribasic acid, $C_{14}H_{18}O_6$, must be represented as (XV). The second tribasic acid, $C_{15}H_{20}O_6$, was formulated as (XVI), but it was not possible to suggest a formula for the dibasic acid, $C_{11}H_{18}O_4$, which must be monocyclic, so that ring fission is involved in its formation.



The data available are insufficient to provide rigorous proof of the structure of longifolene, but they limit very considerably the number of possible formulae, if it be assumed that the structure of the hydrocarbon is built up in accordance with the isoprene rule. Bradfield, Francis and Simonsen suggested that, of the possible tricyclic structures containing only *cyclopentane* and *cyclohexane* rings, the formulae (XVII) and (XVIII) were most suitable, with (XVII) being preferred as it accounts more readily for the formation of the tetracyclic 1-methyldehydro-longifane containing a *cyclopropane* ring (see above).

It was mentioned above (p. 92) that amongst the neutral products of the oxidation with chromic acid was a diketone. This yellow crystalline ketone, *d*-longif-1:2-dione, $C_{15}H_{22}O_2$, m.p. 93–94°, is apparently the only 1:2-diketone belonging to the sesquiterpene series which has been described. It resembles cam-

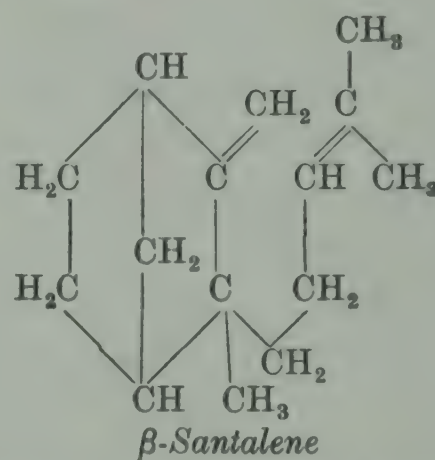
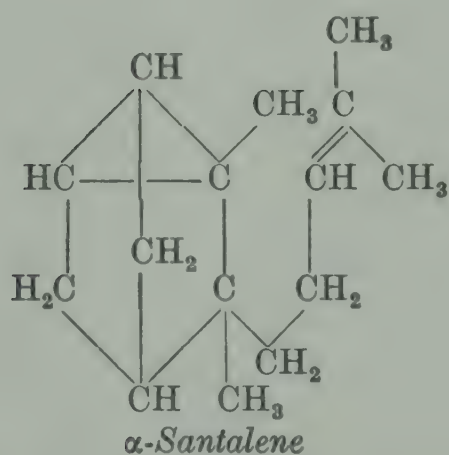


phorquinone very closely in appearance and also in its properties. There can be no doubt that it is a 1:2-diketone, since it gives with *o*-phenylenediamine a *quinoxaline* derivative, m.p. 134°. It has been characterised also by the preparation of a *monosemicarbazone*, m.p. 214–216°, *monophenylhydrazone*, m.p. 129–130°, *mono-p-bromophenylhydrazone*, m.p. 159° and a *mono-oxime*, m.p. 226–227°. Apart from the quinoxaline derivative, no derivatives in which the second carbonyl group has reacted have been prepared, which affords evidence that this must be attached to a tertiary carbon atom. On reduction with zinc dust, it yields a ketonic alcohol, *d-longif-1-ol-2-one*, m.p. 115–117°, $[\alpha]_D + 100.8^\circ$, *acetyl* derivative, m.p. 90–91°. The diketone is not attacked by potassium permanganate or hydrogen peroxide and it cannot be brominated, but, when treated with a mixture of nitric and sulphuric acids, ring fission occurs with the formation of a dibasic acid, 1- α -longiforic acid, C₁₅H₂₄O₂, m.p. 225–227°, $[\alpha]_D - 23.47^\circ$, *dimethyl ester*, m.p. 94–95°. α -Longiforic acid yields an anhydride and is isomerised when heated with hydrogen bromide at 140° to 1- β -longiforic acid, m.p. 197–198°, $[\alpha]_D - 49.3^\circ$. This acid does not give an anhydride and, although the relationship of the two acids has not been proved, it appears probable that they are *cis-trans*-isomerides. The resemblance of *d*-longif-1:2-dione to camphorquinone is shown in the behaviour of its mono-oxime on

treatment with benzenesulphonyl chloride in pyridine solution, when it gives a mixture of an *anhydride*, $C_{30}H_{44}O_3N_2$, m.p. $182-183^\circ$, and a *cyano-acid*, $C_{15}H_{23}O_2N$, m.p. 127° (compare Vol. II, p. 473).

The relationship of this diketone to longifolic acid has not been determined and it is of course possible that they do not originate from the same hydrocarbon. This possibility is enhanced by the very small yield of the diketone which is obtained. It is, indeed, difficult to account for the formation of a diketone from a hydrocarbon having the group, $—CH:CH_2$, in the side chain, although it could result from an α -hydroxy acid in a manner analogous to the conversion of α -fenchocarboxylic acid into carbofenchonone (see Vol. II, p. 578).

THE SANTALENES



Owing to the pharmacological importance which was formerly attributed to it, East Indian sandalwood oil, obtained from the wood of *Santalum album*, has been very thoroughly investigated and it has been shown to contain a large number of substances, the majority of which have a very close structural relationship with one another. For our knowledge of the chemistry of this oil we are indebted mainly to the investigations of Soden and Müller,* Guerbet,[†] Semmler and his collaborators,[‡] Ruzicka and his collaborators,[§] Schimmel and Co.,^{||} and Guha and Bhattacharyya.[¶]

* *Arch. Pharm.* 1900, **238**, 353.

[†] *Compt. rend.* 1900, **130**, 417, 1324.

[‡] *Ber.* 1907, **40**, 1120, 1124, 3321, 4465, 4594; 1908, **41**, 125, 385; 1910, **43**, 445, 1723, 1893; 1911, **44**, 462; 1913, **46**, 2306; 1914, **47**, 1153, 2080; 1916, **49**, 2563.

[§] *Helv. Chim. Acta*, 1926, **9**, 140; 1935, **18**, 355.

^{||} *Schimmel's Report*, 1910, Oct., p. 121.

[¶] *J. Ind. C.S.* 1944, **21**, 261, 271, 281, 333, 339, 341.

It will be convenient to tabulate here the more important constituents of the oil:

(I). *Hydrocarbons*

Santene, C_9H_{14} (Vol. II, p. 243)

Nortricycloekasantalane, $C_{11}H_{18}$ (p. 106)

α -Santalene, $C_{15}H_{24}$

β -Santalene, $C_{15}H_{24}$

(II). *Alcohols*

Santenol, $C_9H_{16}O$ (Vol. II, p. 251)

Teresantalol, $C_{10}H_{16}O$ (Vol. II, p. 264)

α -Santalol, $C_{15}H_{24}O$ (p. 180)

β -Santalol, $C_{15}H_{24}O$ (p. 185)

(III). *Aldehyde*

Nortricycloekasantalal, $C_{11}H_{16}O$ (p. 196)

(IV). *Ketones*

Santenone, $C_9H_{14}O$ (Vol. II, p. 257)

Santalone, $C_{11}H_{16}O$ (p. 106)

(V). *Acids*

Teresantalic acid, $C_{10}H_{14}O_2$ (Vol. II, p. 264)

β -Santalic acid, $C_{15}H_{22}O_2$ (p. 106)

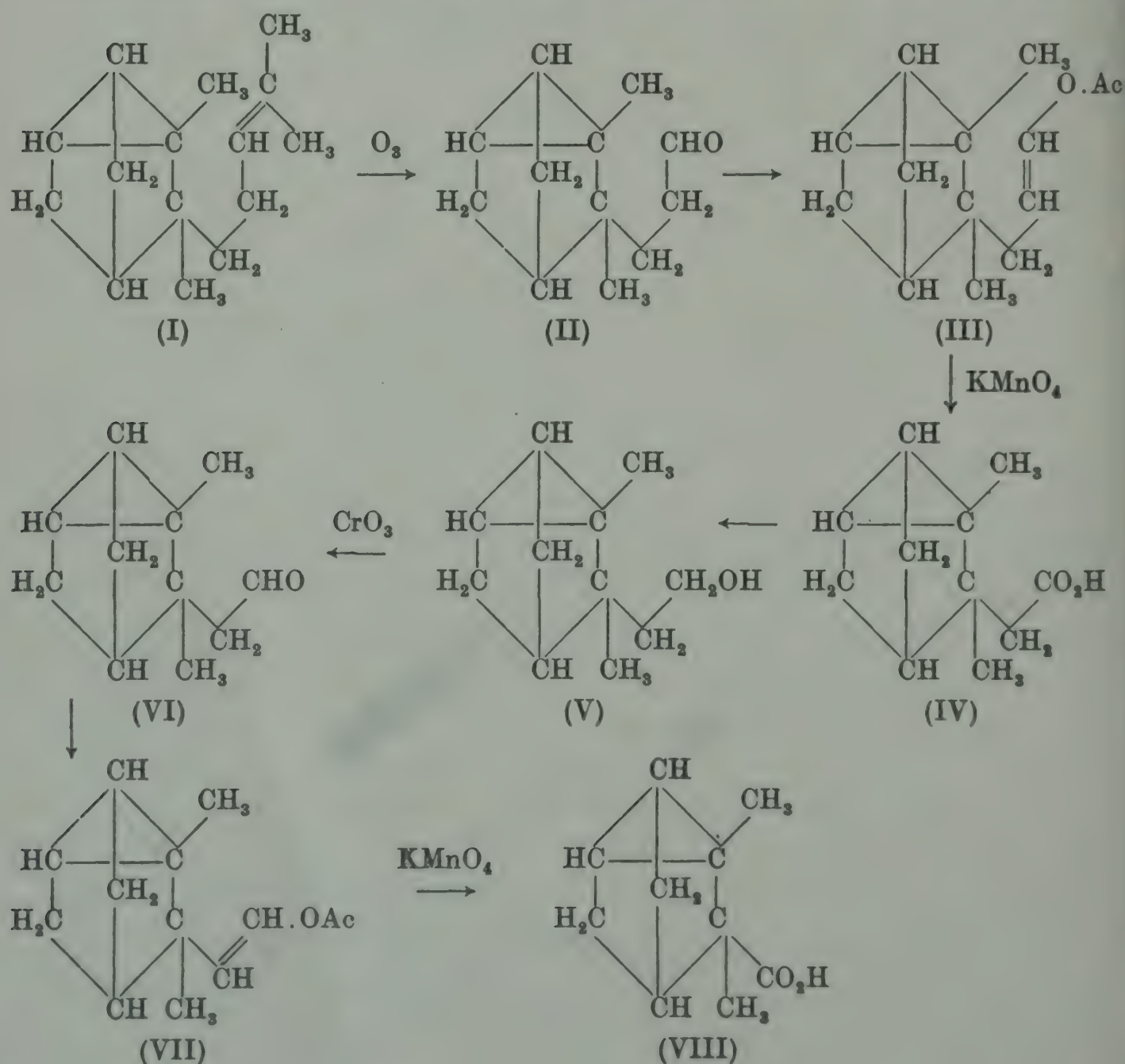
γ -Santalic acid, $C_{15}H_{22}O_2$ (p. 107)

The two sesquiterpenes present in sandalwood oil, which are designated α - and β -santalenes, can only be separated from one another by prolonged fractional distillation, and it is therefore doubtful if either of them has been obtained pure. Guerbet was the first to recognise that the sesquiterpene fraction of sandalwood oil was not homogeneous, and from the lower boiling fraction, α -santalene, he prepared a *nitrosochloride*, m.p. 122° , and from the higher boiling fraction, β -santalene, two *nitrosochlorides*, m.p.s 152° and 106° .

α -Santalene, b.p. $117^\circ/7$ mm., $d_4^{20^\circ}$ 0.9102, $n_D^{20^\circ}$ 1.4900, $\alpha_{5780} + 2.06^\circ$, is tricyclic and a derivative of teresantalic acid. Its constitution has been conclusively established by Semmler's prolonged investigations.

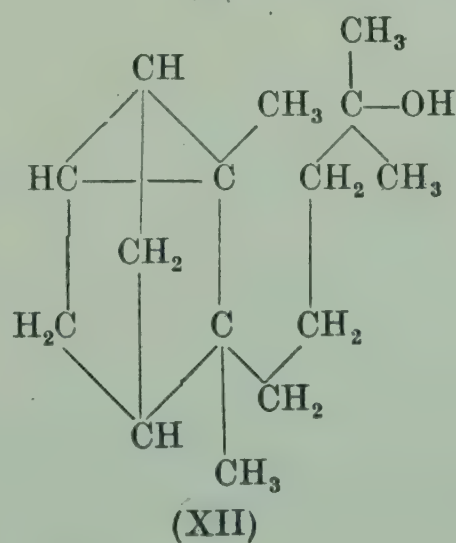
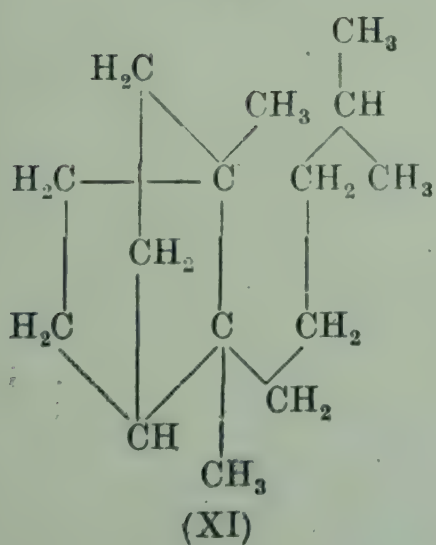
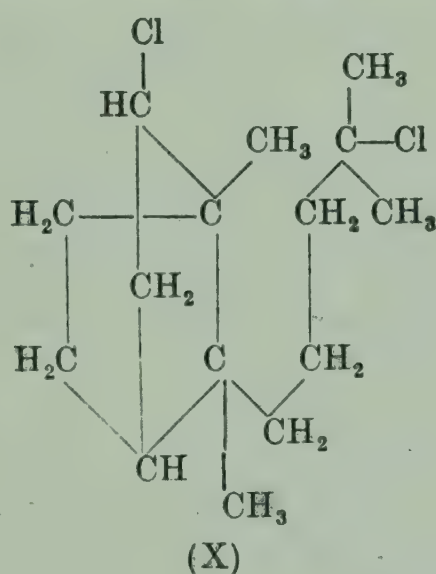
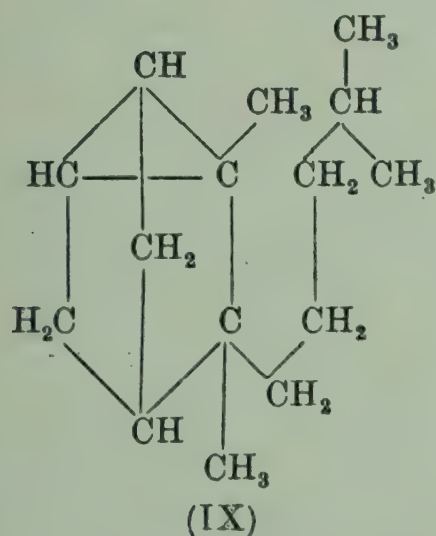
When α -santalene is oxidised with ozone it yields an aldehyde, *tricycloekasantalal* (II), $C_{12}H_{18}O$, b.p. $109-110^{\circ}/10$ mm.; d^{20}_{20} 0.9845 , n_D 1.4852 , α_D $+13.30^{\circ}$, *semicarbazone*, m.p. 156° , which must contain the grouping, $-\underset{|}{\text{CH}}\cdot\text{CHO}$ or $-\text{CH}_2\cdot\text{CHO}$, since,

when it is treated with sodium acetate and acetic anhydride, it yields the *enol-acetate* of *tricycloekasantalal* (III), b.p. $130-132^{\circ}/10$ mm. This acetate, on oxidation with potassium permanganate in acetone solution, gives *nortricycloekasantalic acid* (IV), m.p. 93° , b.p. $143-145^{\circ}/10$ mm. If *methyl nortricycloekasantalate* is reduced with sodium in alcoholic solution an alcohol, *nortricycloekasantanol* (V), $C_{11}H_{18}O$, b.p. $114-117^{\circ}/10$ mm., d^{20}_{20} 0.9558 , n_D 1.4905 , $[\alpha]_D$ -0.7° , is obtained, which, on oxidation with potassium dichromate and sulphuric acid, gives *nortricycloekasantalal* (VI), $C_{11}H_{16}O$, b.p. $91-94^{\circ}/11$ mm., d^{20}_{20} 0.9964 ,



n_D 1.4830, $[\alpha]_D - 30.8^\circ$, *semicarbazone*, m.p. 224° . This aldehyde was degraded in exactly the same manner as *tricycloekasantalal*. By the action of sodium acetate and acetic anhydride it was converted into the *enol-acetate* (VII), b.p. $110-113^\circ/10$ mm., d^{20° 1.0270, n_D 1.4837, $[\alpha]_D - 25.67^\circ$, and this, on oxidation with potassium permanganate, gave *teresantallic acid* (VIII) (see Vol. II, p. 264). From this series of reactions and the relationship of the hydrocarbon to α -santalol, the structure of which has now been rigidly established (see p. 180), it follows that α -santalene must be represented by (I).

α -Santalene can be readily hydrogenated in the presence of platinum black to *dihydro- α -santalene* (IX), d^{20° 0.899, n_D 1.495.* On treatment with hydrogen chloride it yields a liquid *dihydrochloride*, b.p. $140-142^\circ/0.55$ mm., d^{20° 1.076, n_D 1.4976, probably represented by (X). This chloride, on reduction with sodium in alcoholic solution, gives a *tetrahydrosantalene*, $C_{15}H_{28}$, b.p. $116-118^\circ/9$ mm., d^{20° 0.864, n_D 1.4676, $\alpha_D + 7.30^\circ$, which is probably

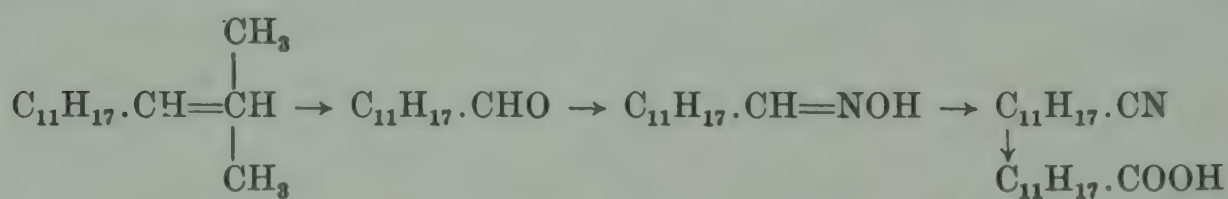


* Semmler and Jakubowicz, *Ber.* 1914, 47, 1153.

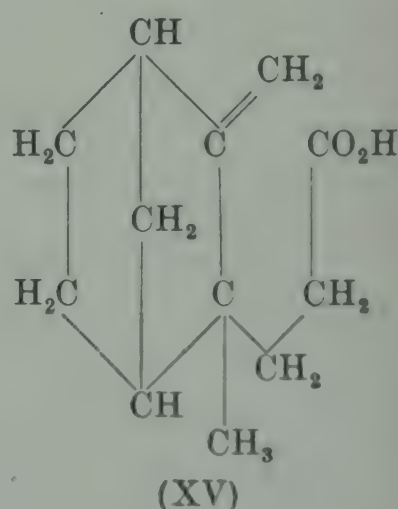
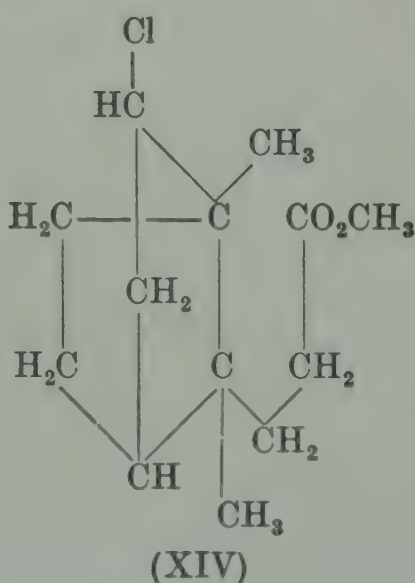
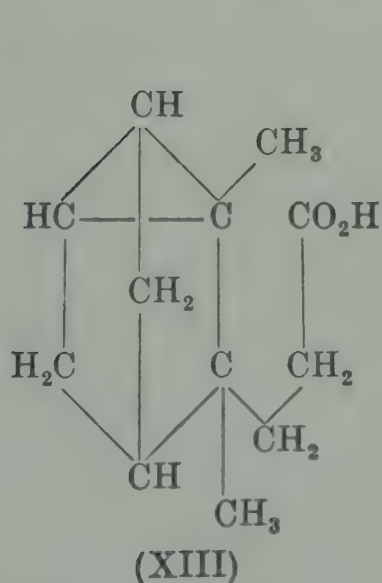
correctly formulated as (XI). When the dihydrochloride is treated with alkali, a sesquiterpene is obtained which is possibly identical with β -santalene (see below). On hydration, α -santalene furnishes a tertiary *alcohol* (XII), b.p. 154–157°/5 mm., d^{15° 0.9787, n_D 1.5173, which can be dehydrated with formic acid to a sesquiterpene, which is not identical with α -santalene. α -Santalene does not yield a naphthalene hydrocarbon on dehydrogenation with sulphur.

β -Santalene boils at 125°/7 mm., $d_4^{20^\circ}$ 0.8940, $n_D^{20^\circ}$ 1.4941, $\alpha_{5780} - 49.9^\circ$,* and from its physical constants must be a dicyclic hydrocarbon. This is borne out by its reactions, which are discussed below.

When β -santalene is oxidised with ozone† it yields an aldehyde, *ekasantalal*, $C_{12}H_{18}O$, which has not been obtained pure, but which can be converted through its oxime into an acid, *ekasantalic acid*, $C_{12}H_{18}O_2$. These reactions may be represented by the scheme:



Ekasantalic acid was found to be identical‡ with an acid which had been prepared by Semmler and Bode§ from *tricycloekasantalic acid*. This latter acid, m.p. 71–72°, b.p. 163–165°/9.5 mm.,



* Guha and Bhattacharyya, *J. Ind. C.S.* 1944, 21, 261.

† Cf. Bhattacharyya, *Science and Culture*, 1947, 13, 206.

‡ Cf. Bhattacharyya, *Science and Culture*, 1947, 13, 158, 159, 207.

§ *Ber.* 1907, 40, 1139; Semmler, *ibid.* p. 3321; the composition of *tricycloekasantalic acid*, m.p. 71–72°, is $C_{12}H_{18}O_2$, and not $C_{11}H_{16}O_2$, as given in this paper (compare Semmler, *ibid.* 1910, 43, 1898).

d^{15° 1.0482, n_D 1.4938, is obtained when α -santalol (p. 180) is oxidised with either potassium permanganate or ozone. Its constitution must be represented by (XIII), since it can be converted into tricycloekasantalal (II) and has been synthesised from *d*-camphor *via* teresantalol.*

When tricycloekasantalic acid is treated in methyl alcoholic solution with hydrogen chloride, it yields the *chloride* of a *methyl ester*, $C_{13}H_{21}O_2Cl$ (probably (XIV)), b.p. 154–158°/10 mm., d^{15° 1.103, $n_D^{15^\circ}$ 1.4967, $\alpha_D + 16^\circ$, fission of the *cyclopropane* ring having accompanied the esterification. This ester, when warmed with an alcoholic solution of potassium hydroxide, gave an unsaturated acid, *ekasantalic acid*, m.p. 64°, b.p. 168–169°/10.5 mm., d^{25° 1.058, n_D 1.5033, $[\alpha]_D + 41.81$, identical with that obtained by the oxidation of β -santalene. This last step must involve a Wagner rearrangement, for Ruzicka and Thomann† have provided convincing evidence that ekasantalic acid must be represented by (XV). Thus on ozonolysis of ekasantalic acid *camphenilonylacetic acid* (XVI), $C_{11}H_{16}O_3$, b.p. 149°/0.1 mm., *methyl ester*, m.p. 76–77° (*semicarbazone*, m.p. 192°), and β -(*methylnorcampholidyl*)-*propionic acid* (XVII), $C_{11}H_{16}O_4$, b.p. ca. 180°/0.1 mm., *methyl ester*, b.p. 132°/0.1 mm., $d_4^{22^\circ}$ 1.150, $n_D^{22^\circ}$ 1.483, were obtained. The double bond in ekasantalic acid must be present therefore as an exocyclic methylene group as in camphene (Vol. II, p. 286), where ozonolysis affords in a similar manner camphenilone and dimethylnorcampholide. Ruzicka and Thomann also obtained the lactonic acid (XVII) by the ozonolysis of a crude β -santalene. There is strong evidence from these experiments that the formula (XVIII) correctly represents the properties of β -santalene.‡

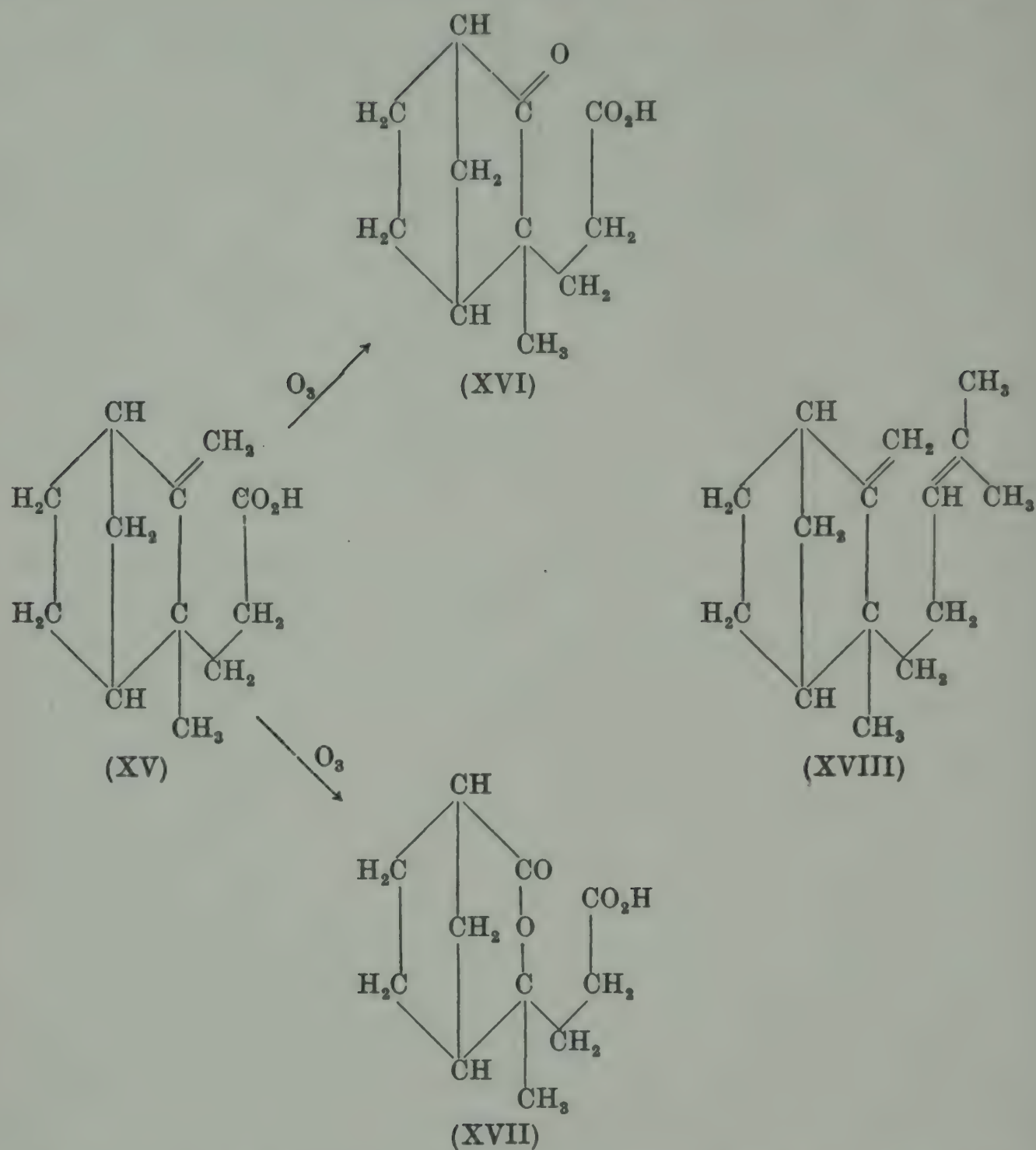
Both ekasantalic acid and tricycloekasantalic acid furnish the same *lactone*, $C_{12}H_{18}O_2$, m.p. 103–104°, on boiling with formic acid. If the correct formula for the lactone prepared by Semmler and Bartelt§ from teresantallic acid in an exactly similar manner be (XIX) (see Vol. II, p. 268), then it would appear possible that the lactone, $C_{12}H_{18}O_2$, is best represented by (XX), the

* Guha and Bhattacharyya, *J. Ind. C.S.* 1944, **21**, 271.

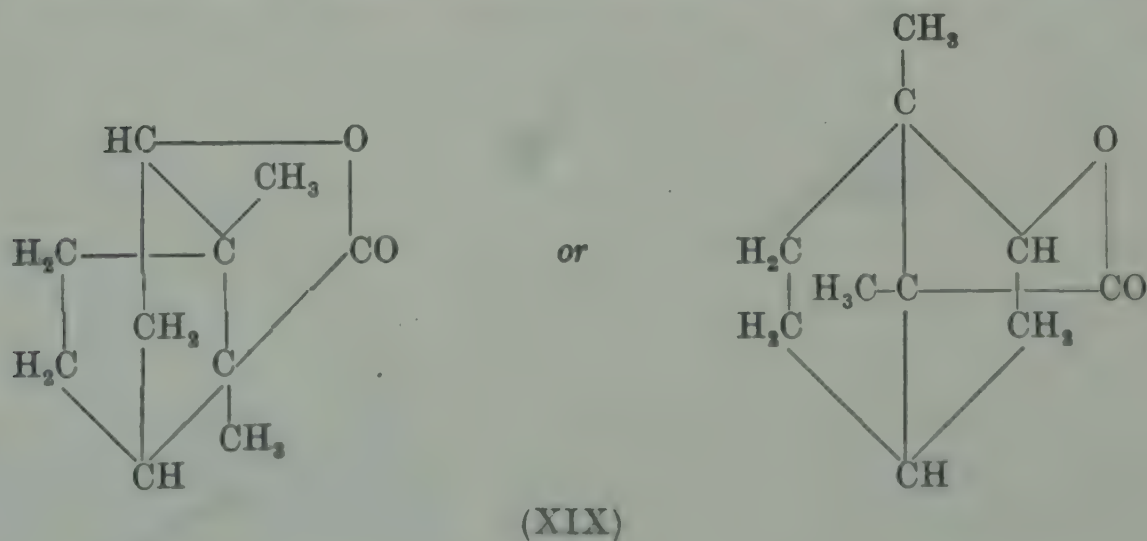
† *Helv. Chim. Acta*, 1935, **18**, 355.

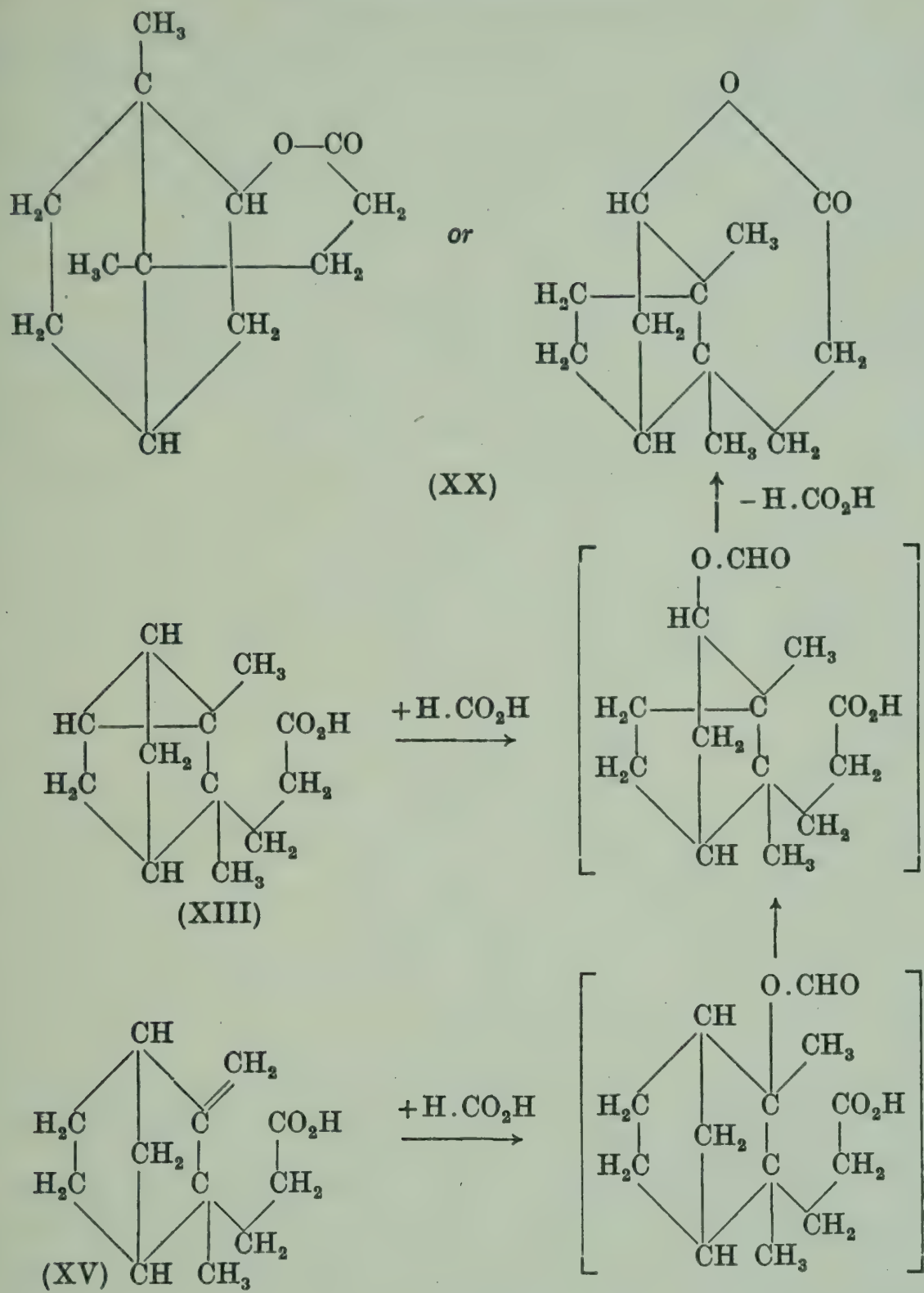
‡ Compare the formula now assigned to *isoteresantallic acid* (Vol. II, p. 269) which is obtained from teresantallic acid in the same way that ekasantalic acid originates from tricycloekasantalic acid.

§ *Ber.* 1907, **40**, 4469.



mechanism of its formation, which involves a Wagner rearrangement in the case of ekasantalic acid, being shown in the scheme:



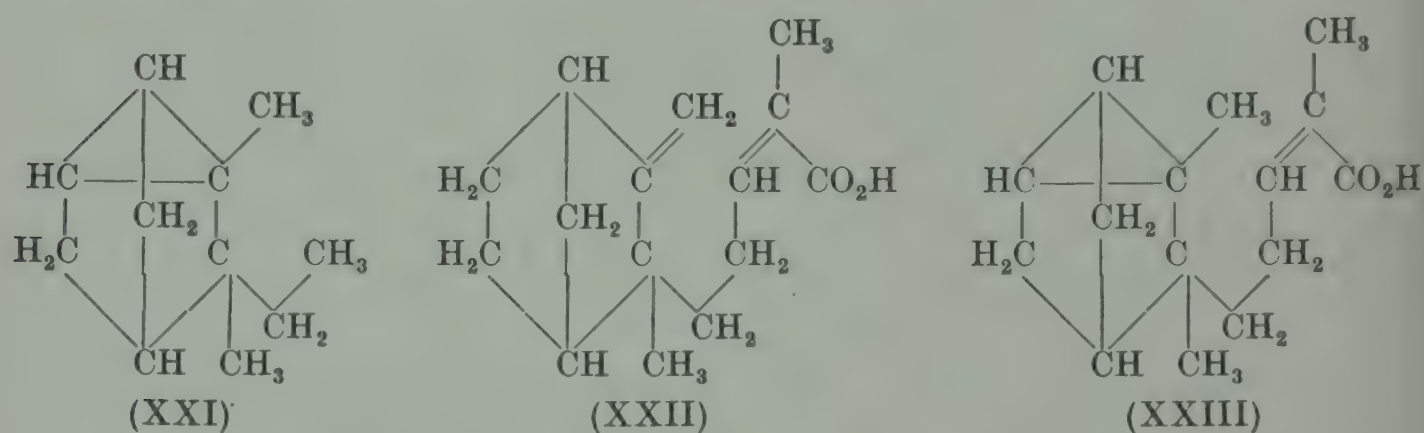


β -Santalene can be characterised by the preparation of the two *nitrosochlorides* mentioned above (p. 99). It gives with hydrogen chloride a *dihydrochloride*, identical probably with that prepared from α -santalene.* It cannot be dehydrogenated to a naphthalene hydrocarbon with sulphur.† On hydration by the Bertram-Walbaum method β -santalene yields an *alcohol*, C₁₅H₂₆O, b.p. 160–165°/6 mm., d^{15° 0.978.‡

* Guerbet, *Compt. rend.* 1900, 130, 1324; Semmler, *Ber.* 1910, 43, 446.
† Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, 6, 854.
‡ Soden and Müller, *Arch. Pharm.* 1900, 238, 263.

Semmler and Jonas* have prepared a hydrocarbon, which they suggest is identical with β -santalene, by heating a mixture of isoprene and β -phellandrene under pressure. Their identification was based solely on the evidence of a resemblance in physical properties and was not supported by the preparation of any derivatives.

The low boiling fraction of sandalwood oil contains a hydrocarbon, $C_{11}H_{18}$, b.p. 183° , d^{20}_D 0.9092, n^{20}_D 1.4786, $\alpha_D -23.55^\circ$, which Schimmel and Co.† suggest is identical with *nortricycloekasantalane* (XXI), b.p. 183.5° , d^{20}_D 0.885, n^{20}_D 1.4686, $\alpha_D -11^\circ$, which was prepared by Semmler and Bode‡ by the distillation of the ozonide of α -santalol under diminished pressure. The identity has not been definitely established, but would appear probable. The hydrocarbon is very stable and cannot be hydrated.



Soden and Müller§ separated from East Indian sandalwood oil a ketone, *santalone*, $C_{11}H_{16}O$, b.p. $214-215^\circ$, d^{15}_D 0.9906, n_D 1.5002, $\alpha_D -60^\circ$, and its occurrence in the oil has been confirmed by Schimmel and Co.¶ The ketone yields a crystalline *oxime*, m.p. $74-75^\circ$, and a *semicarbazone*, m.p. $174-176^\circ$. Its constitution and its relationship to the other constituents have not been determined.

Sandalwood oil contains at least two other acids besides tere-santallic acid. A bicyclic, doubly unsaturated *acid*, $C_{15}H_{22}O_2$, b.p. $181^\circ/1$ mm., n^{20}_D 1.5136, was isolated by Bhattacharyya‡ who named it β -santallic acid (XXII), and considered it to be a derivative of β -santalol on account of the physical properties of

* *Ber.* 1914, **47**, 2080.

† *Schimmel's Report*, 1910, Oct., p. 121.

§ *Arch. Pharm.* 1900, **238**, 366.

¶ *Schimmel's Report*, 1910, Oct., p. 125.

‡ *Ber.* 1907, **40**, 1137.

§ *J. Ind. C.S.* 1944, **21**, 337.

the acid and its *methyl ester*, b.p. $157^{\circ}/9$ mm., $n_D^{25^{\circ}}$ 1.4969, $n_D^{20^{\circ}}$ 1.4989. γ -*Santalal acid* is the name now suggested* for the acid first isolated by Guerbet† and originally called simply *santalal acid*. The physical properties of γ -*santalal acid*, b.p. $189^{\circ}/9$ mm., $n_D^{28.5^{\circ}}$ 1.5021, $n_D^{20^{\circ}}$ 1.5055, and of its *methyl ester*, b.p. $141^{\circ}/9$ mm., $d_4^{20^{\circ}}$ 1.0286, $n_D^{20^{\circ}}$ 1.4915, suggest that it may be tetracyclic. The name α -*santalal acid* should be reserved for the compound (XXIII) first prepared by Semmler‡ by oxidation of α -*santalol* and having b.p. $193^{\circ}/9$ mm., $n_D^{20^{\circ}}$ 1.5055, *methyl ester*, b.p. $146^{\circ}/9$ mm., $d_4^{20^{\circ}}$ 1.0021, $n_D^{20^{\circ}}$ 1.4910. It is not a constituent of sandalwood oil itself.§

D. HYDROCARBONS OF UNKNOWN CONSTITUTION

CALAMENE

The oil derived from the rhizomes of *Acorus Calamus* L. contains a sesquiterpene, *calamene*, which was probably first separated in a pure condition by Kurbatov,|| although its occurrence had been observed by Gladstone.¶

Calamene, $C_{15}H_{24}$, b.p. 123 – $126^{\circ}/10.5$ mm., $d_{19}^{20^{\circ}}$ 0.9224, $n_D^{20^{\circ}}$ 1.5057, $[\alpha]_D + 5^{\circ}$, does not yield any crystalline derivatives and it cannot be hydrated. From its physical constants, it was assumed that *calamene* was tricyclic, but Semmler and Spornitz** found that, on catalytic hydrogenation, *tetrahydrocalamene*, $C_{15}H_{28}$, b.p. 123 – $125^{\circ}/10$ mm., $d_{19}^{20^{\circ}}$ 0.8951, $n_D^{20^{\circ}}$ 1.4848, was formed, which indicated the presence of two ethylenic linkages. This evidence cannot, however, be considered conclusive, since it is well known that in many cases the *cyclopropane* ring readily undergoes fission on reduction. Support, however, is lent to the view that *calamene* contains two ethylenic linkages by the observation of Ruzicka, Meyer and Mingazzini†† that, on

* Guha and Bhattacharyya, *J. Ind. C.S.* 1944, **21**, 333.

† *Compt. rend.* 1900, **130**, 417.

‡ *Ber.* 1907, **40**, 1120, 1124

§ The formulae assigned to the α - and β -*santalal acids* have been confirmed by Bhattacharyya (*Science and Culture*, 1947, **13**, 208, 209) by a partial synthesis.

|| *Annalen*, 1874, **173**, 4.

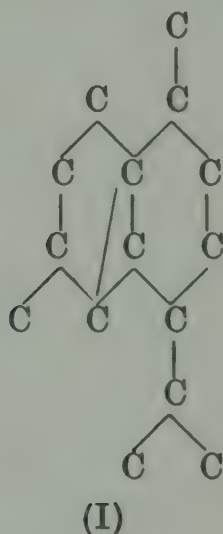
¶ *J.C.S.* 1864, **17**, 1.

** *Ber.* 1913, **46**, 3702.

†† *Helv. Chim. Acta*, 1922, **5**, 358.

dehydrogenation with sulphur, cadalene is formed. As a general rule tricyclic hydrocarbons cannot be dehydrogenated with this reagent.

Recently the nature of calamene has been investigated in some detail by Šorm and Herout,* who conclude that it is actually a mixture of a bicyclic hydrocarbon, α -calamene (80 per cent.), containing two ethylenic linkages and of a tricyclic hydrocarbon, β -calamene (20 per cent.), containing three ethylenic linkages.† This was proved by careful catalytic hydrogenation experiments and by per-acid titration. Dehydrogenation of the mixture of α - and β -calamenes afforded cadalene as noted previously (see above) and S-guaiazulene (p. 7). It is probable therefore that the tricyclic β -calamene has the carbon skeleton indicated in (I).



THE COSTENES

From oil of costus, which is obtained from the roots of *Saussurea Lappa*, Semmler and Feldstein‡ isolated two sesquiterpenes, which they designated α - and β -costene.

α -Costene, $C_{15}H_{24}$, b.p. $122-126^\circ/12$ mm., d^{21}_D 0.9014, n^{16}_D 1.49807, $[\alpha]_D -12^\circ$, is probably dicyclic and gives a liquid hydrochloride, from which the original hydrocarbon can be regenerated. It is readily hydrated by the Bertram-Walbaum method yielding an *alcohol*, $C_{15}H_{26}O$, b.p. $150-165^\circ/14.5$ mm., d^{21}_D 0.9491, n_D 1.5000, $[\alpha]_D +20^\circ$, which suggests that one of the ethylenic linkages is exocyclic.

* *Coll. Czech. Chem. Comm.* 1948, **13**, 177.

† Compare Asahina and Imai, *Schimmel's Report*, 1915, Oct., p. 8.

‡ *Ber.* 1914, **47**, 2692.

β -Costene, b.p. 144–149°/18 mm., d^{22° 0.8728, n_D 1.4905, $[\alpha]_D + 6^\circ$, is probably monocyclic, but no crystalline derivatives have been prepared. There is no evidence of the homogeneity of either α - or β -costene. It is of interest to mention that associated with these sesquiterpenes is an acyclic hydrocarbon, *aplotaxene*, $C_{17}H_{28}$, which gives on catalytic hydrogenation *octahydroaplotaxene*, identical probably with *n*-heptadecane.

THE GURJUNENES

Gurjun balsam, an oleo-resin derived from various species of *Dipterocarpus*, yields an oil, which was shown by Deussen* to be a mixture of sesquiterpenes. By prolonged fractional distillation of the oil Deussen and Philipp† separated two sesquiterpenes, α - and β -gurjunenes,‡ the former of which was *laevorotatory* and the latter *dextrorotatory*.

These sesquiterpenes were investigated by Semmler and Jakubowicz,§ who showed them both to be tricyclic. It is not possible to separate them completely by fractional distillation, but a fairly pure α -gurjunene, $C_{15}H_{24}$, b.p. 114–116°/10 mm., d^{20° 0.918, n_D 1.5010, $\alpha_D - 95^\circ$, can, according to Treibs,|| be obtained in this manner. Pfau and Plattner¶ have recorded a somewhat higher boiling-point for the hydrocarbon, which they do not regard as completely homogeneous. They give b.p. 127–128°/10 mm., d^{20° 0.9140, $n_D^{20^\circ}$ 1.5010, $\alpha_D - 179.5^\circ$. Although the density and refractive index are in good agreement with those reported by Treibs, Pfau and Plattner consider that the molecular refraction indicates a doubly unsaturated, bicyclic sesquiterpene rather than a mono-unsaturated, tricyclic compound. $[R_L]_D$ found, Treibs 65.45, Pfau and Plattner 65.82; $C_{15}H_{24}$, 2 ϵ requires 66.13, $C_{15}H_{24}$, 1 ϵ requires 64.40. Clearly further study of α -gurjunene is required to reconcile these conflicting viewpoints.

* *Annalen*, 1909, 369, 56.

† *Ibid.* 1910, 374, 105.

‡ Mitter and Palit (*Proc. Ind. Sci. Cong.* 1927, p. 161) have described a tricyclic hydrocarbon, *inene*, which they separated from the oleo-resin of *D. tuberculatus*. Since the hydrocarbon gives the Turner colour reaction it is probably identical with α -gurjunene.

§ *Ber.* 1914, 47, 1029, 1144, 2253.

|| *Ibid.* 1935, 68, 1751.

¶ *Helv. Chim. Acta*, 1936, 19, 858.

On heating α -gurjunene with sulphur, selenium, or nickel or simply by the action of heat alone, an azulene is obtained, which Pfau and Plattner* have shown to be identical with *S-guaiazulene* (I) (see p. 7). On catalytic reduction, α -gurjunene furnished the saturated hydrocarbon *dihydro- α -gurjunene*, d^{20° 0.8977, n_D 1.4897, α_D -18° . From this fact and the marked exaltation of the molecular refraction of the parent α -gurjunene it was inferred that the double bond was probably in conjugation with a cyclopropane ring as in sabinene (Vol. II, p. 19) and aromadendrene (p. 71). However, α -gurjunene gave only a *mono-hydrochloride*, b.p. $165-170^\circ$, d^{20° 1.029 on treatment with hydrogen chloride in acetic acid solution, from which α -gurjunene could be regenerated substantially unchanged by boiling with alcoholic potassium hydroxide. On treatment with hot acetic acid-sulphuric acid mixture α -gurjunene was isomerised to the dicyclic iso- α -gurjunene, d^{20° 0.9109, n_D 1.5101, α_D -135° , which, from the exaltation of the molecular refraction and the ease of catalytic reduction to *tetrahydroiso- α -gurjunene*, d^{20° 0.875, n_D 1.4765, α_D -10° , must contain two double bonds in conjugation.[†] A dicyclic *hydrocarbon* or mixture of hydrocarbons, b.p. $123-129^\circ/12$ mm., $d_4^{15^\circ}$ 0.9233, $n_D^{15^\circ}$ 1.5105, α_D -39° , is also stated to be formed when α -gurjunene hydrochloride is heated with sodium acetate in acetic acid solution[‡] and this substance also takes up two molecular proportions of hydrogen on catalytic reduction to afford a saturated *hydrocarbon*, $C_{15}H_{28}$, b.p. $125-130^\circ/12$ mm., $d_4^{15^\circ}$ 0.9021, $n_D^{15^\circ}$ 1.4910.

When α -gurjunene is oxidised with hot aqueous potassium permanganate, oxalic and acetic acids are produced but no acetone or formaldehyde, whilst with potassium permanganate in acetone solution oxalic acid and a relatively large amount of succinic acid are formed. If the crude acid product from this treatment is oxidised further with nitric acid, a liquid tricarbonylic acid, $C_9H_{14}O_6$, *trimethyl ester*, b.p. $165-167^\circ/20$ mm., d^{20° 1.148, n_D 1.4435, α_D $\pm 0^\circ$, which is not identical with camphoronic acid, is said to result.[§] From hydrolysis experiments it appears that one of the carboxyl groups in this acid is attached

* *Helv. Chim. Acta*, 1936, 19, 858.

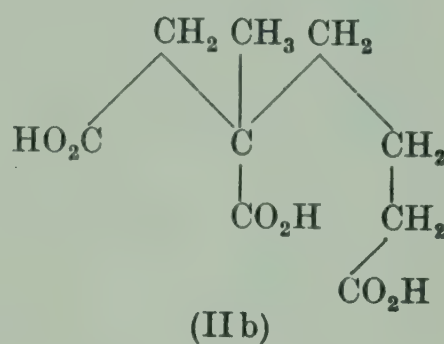
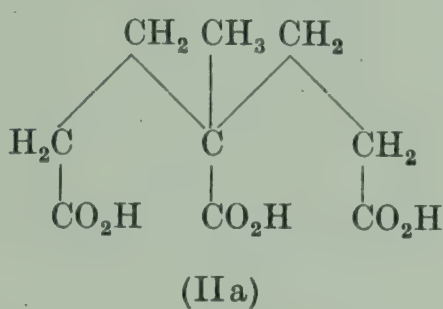
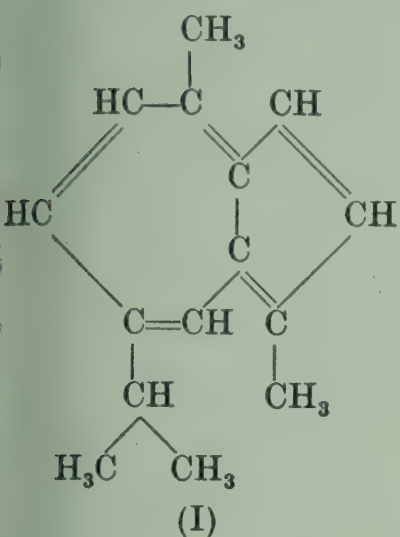
† Treibs, *loc. cit.*

‡ Ruzicka, Pontalti and Balas, *Helv. Chim. Acta*, 1923, 6, 864.

§ Treibs, *loc. cit.*

to a quaternary carbon atom, whereas the other two acid groups must be attached to secondary carbon atoms.

Treibs suggests that this acid may be represented by either (IIa) or (IIb), but in the absence of any proof of its structure it would appear premature to suggest a formula for α -gurjunene which, at the present time, must be based essentially on its dehydrogenation to S-guaiazulene (I).



β -Gurjunene, $C_{15}H_{24}$, can readily be separated from α -gurjunene by taking advantage of the fact, first observed by Semmler and Jakubowicz, that if the sesquiterpene mixture is oxidised first with chromic acid and then with potassium permanganate in acetone solution until no further change in rotatory power can be observed, the α -gurjunene is completely removed and pure β -gurjunene recovered. The hydrocarbon obtained in this manner has b.p. $120-123^\circ/13$ mm., d^{20}_D 0.9348, n_D 1.5028, $\alpha_D + 74.5^\circ$, constants very similar, except for the optical rotatory power, to those of cedrene (p. 75). On oxidation with either chromic acid or potassium permanganate it yields a *ketone*, $C_{15}H_{22}O$, m.p. 43° , b.p. $163-166^\circ/10$ mm., d^{20}_D 1.017, n_D 1.5270, $\alpha_D + 123^\circ$, *semicarbazone*, m.p. 243° , which gives an unsaturated secondary *alcohol*, m.p. 104° , b.p. $155-159^\circ/11$ mm., d^{20}_D 1.001, n_D 1.5186, $\alpha_D + 34^\circ$, on reduction with sodium and alcohol. From the semicarbazone of the ketone, β -gurjunene can be regenerated by the Kishner-Wolff reaction. Although the physical constants of this ketone and of the alcohol are very similar to those of cedrenone and *sec.*-cedrenol respectively (see p. 78), they are definitely not identical as is shown by a comparison of their optical rotatory powers. Possibly α -cedrene and β -gurjunene are

related as enantiomorphs, but there is no definite evidence that this is the case.

On catalytic hydrogenation, β -gurjunene gives the saturated hydrocarbon, *dihydro- β -gurjunene*, b.p. $120^{\circ}/8$ mm., d_{20}^{20} 0.9172, n_D 1.4922, α_D -42° . By the action of hydrogen chloride in acetic acid solution it is isomerised to *iso- β -gurjunene*, d_{20}^{20} 0.9313, n_D 1.5109, α_D -36° , which contains two double bonds not in conjugation and which can be reduced catalytically to *tetrahydroiso- β -gurjunene*, d_{20}^{20} 0.9046, n_D 1.4870, α_D -15° . Like most other tricyclic sesquiterpenes, β -gurjunene does not give a naphthalene hydrocarbon on dehydrogenation with sulphur.* When it is heated in a sealed tube at 330° for some hours it is decomposed, yielding α -terpinene and a diterpene, $C_{20}H_{32}$, b.p. $170^{\circ}/10$ mm., d_{20}^{20} 0.9603, n_D 1.5404.† β -Gurjunene does not give the Turner colour reaction when pure, whereas α -gurjunene does.

HUMULENE

In 1895 Chapman‡ separated from oil of hops (from *Humulus Lupulus* L.) a sesquiterpene, *humulene*, $C_{15}H_{24}$, which he characterised by the preparation of a number of derivatives. Some years later the same hydrocarbon was shown by Fichter and Katz§ to be present in the oil from poplar buds (*Populus nigra* L.).

Humulene, b.p. $127^{\circ}/12$ mm., d_4^{20} 0.8922, n_D^{20} 1.5022, is somewhat readily oxidised on exposure to the air. It was suggested by Deussen|| that humulene was probably identical with α -caryophyllene (see p. 40) and this has recently been confirmed beyond doubt by Šorm and his collaborators.¶ The latter authors have shown that humulene contains three ethylenic linkages and is, therefore, monocyclic. Hydrogenation afforded the saturated *hexahydrohumulene*, $C_{15}H_{30}$, b.p. 120 – $122^{\circ}/13$ mm., d_4^{20} 0.8637, n_D^{20} 1.4723, whilst treatment with perbenzoic acid gave *humulene trioxide*, $C_{15}H_{24}O_3$, m.p. 122.5° . Ozonolysis of humulene furnished α,α -dimethylsuccinic acid, which had been obtained

* Ruzicka, Pontalti and Balas, *loc. cit.*

† Semmler and Jakubowicz, *Ber.* 1914, **47**, 2254.

‡ *J.C.S.* 1895, **67**, 54, 780.

§ *Ber.* 1899, **32**, 3183.

|| *J. pr. Chem.* 1911 [ii], **83**, 1483; 1928 [ii], **120**, 133; compare Chapman, *J.C.S.* 1928, p. 785; 1929, p. 359.

¶ *Coll. Czech. Chem. Comm.* 1949, **14**, 693, 699, 716.

earlier by Chapman* by chromic acid oxidation of the hydrocarbon.

Humulene may be characterised† by the formation of the *nitrosochloride*, m.p. 176°, the *nitrolbenzylamine*, m.p. 136°, the *nitrolpiperidide*, m.p. 153°, the *nitrosate*, m.p. 163°, and the *nitrosite*, m.p. 114°.

The reduction of humulene nitrosite by sodium and alcohol to *aminodihydrohumulene*, $C_{15}H_{27}N$, b.p. 141–142°/11 mm., $d_{25}^{25^\circ}$ 0.9202, $n_D^{25^\circ}$ 1.5039, $[\alpha]_{5461} -0.64^\circ$, *hydrochloride*, m.p. 257°, *acetyl derivative*, m.p. 142°, *picrolonate*, m.p. 232°, has been described by Evans, Ramage and Simonsen.‡

SESQUICHAMENE

Kafuku and Nozoe§ have isolated from the essential oil obtained from the leaves of *Chamaecyparis obtusa* Sieb. et Zucc. f. *formosana* Hayata, a tricyclic sesquiterpene hydrocarbon, *sesquichamene*, $C_{15}H_{24}$, b.p. 122–123°/12 mm., $d_4^{28^\circ}$ 0.9277, $n_D^{28^\circ}$ 1.5021, $\alpha_D^{28^\circ} -89.85^\circ$, *nitrosochloride*, m.p. 78–79°, *nitrolbenzylamine derivative*, m.p. 165–166°. Sesquichamene on oxidation with potassium permanganate furnished a *glycol*, $C_{15}H_{26}O_2$, m.p. 89–91°, and a *diketone* or *keto-aldehyde*, $C_{14}H_{20}O_2$, *disemicarbazone*, m.p. 233°. On treatment with alcoholic sulphuric acid it gave *isosesquichamene*, b.p. 129–131°, $d_4^{20^\circ}$ 0.9320, $n_D^{21^\circ}$ 1.5109, $\alpha_D^{21^\circ} -8.5^\circ$.

From the above facts it would seem possible that sesquichamene is identical with α -cedrene (p. 75).

VETIVENE

Vetivene is the name given to the mixture of dicyclic and tricyclic hydrocarbons having the composition $C_{15}H_{24}$, which occur in oil of vetiver from *Vetiveria zizanioides* Stapf. This mixture of hydrocarbons, first separated by Gladstone,^{||} has since been examined by Genvresse and Langlois,[¶] Semmler, Risse and

* J.C.S. 1903, 83, 513.

† Chapman, J.C.S. 1928, p. 785; 1929, p. 359.

‡ J.C.S. 1934, p. 1806.

§ Bull. C.S. Japan, 1931, 6, 111.

|| J.C.S. 1872, 25, 3.

¶ Compt. rend. 1902, 135, 1059.

Schröter,* and by Ruzicka, Capato and Huyser.† According to the last-mentioned authors the tricyclic hydrocarbon boils at 126–127°/12 mm., $d_4^{15^\circ}$ 0.9372, $n_D^{15^\circ}$ 1.5143 and the dicyclic at 132–133°/12 mm., $d_4^{15^\circ}$ 0.9339, $n_D^{15^\circ}$ 1.5179. The dicyclic hydrocarbon yields cadalene on dehydrogenation with sulphur but its constitution has not been determined, nor has that of the tricyclic terpene.

In addition to vetivene, the oil contains a mixture of dicyclic and tricyclic primary and secondary alcohols, the *vetivenols*, $C_{15}H_{24}O$, at least two ketones, the α - and β -vetivones (see p. 224), and a tricyclic acid, *vetivenic acid*, $C_{15}H_{22}O_2$. The dicyclic primary alcohol, b.p. 152–154°/12 mm., $d_4^{17^\circ}$ 0.9851, $n_D^{17^\circ}$ 1.5241, is a mixture, since it yields, on dehydrogenation with sulphur, both cadalene and eudalene, whilst the tricyclic alcohol, b.p. 170–172°/12 mm., $d_4^{18^\circ}$ 1.0228, $n_D^{18^\circ}$ 1.5255, $\alpha_D + 29.6^\circ$, did not yield a naphthalene derivative when treated with this reagent.

* *Ber.* 1912, 45, 2347.

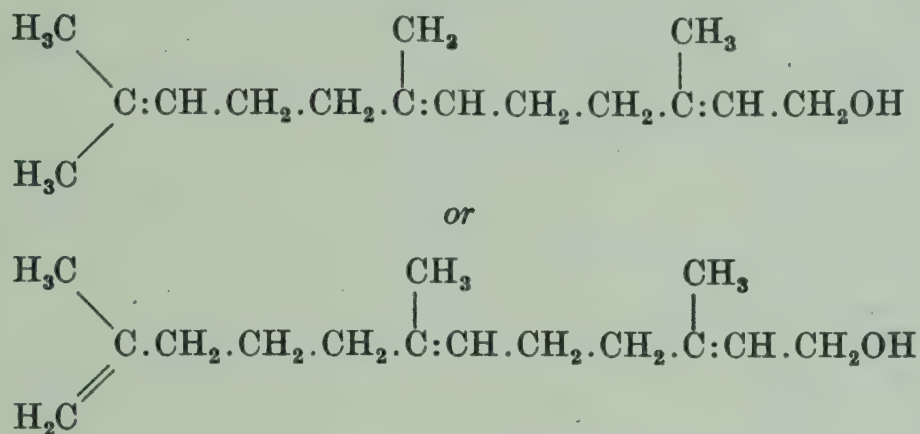
† *Rec. trav. chim.* 1928, 47, 370.

CHAPTER II

ALCOHOLS

A. ACYCLIC ALCOHOLS

FARNESOL



In 1904 Haarmann and Reimer* reported the presence in oil of ambrette seeds (from *Abelmoschus moschatus* Moench) of a sesquiterpene alcohol, farnesol, $\text{C}_{15}\text{H}_{26}\text{O}$. This alcohol has been found since to occur somewhat widely distributed in nature. It has been isolated from citronella oil,[†] palmarosa oil,[‡] rose oil,[§] neroli oil,^{||} oil of *Robinia Pseudacacia*,[¶] and Seville orange oil.**

A consideration of its physical constants, more especially its low density, indicated that farnesol was an acyclic alcohol and must therefore contain three ethylenic linkages. This has been confirmed by the investigations of Kerschbaum,^{††} who has determined its constitution.

Farnesol must be a primary alcohol, since it forms a hydrogen phthalate by the action of phthalic anhydride in benzene solution and, on oxidation with chromic acid mixture, it gives an aldehyde, *farnesal*, $\text{C}_{15}\text{H}_{24}\text{O}$, b.p. $173\text{--}174^\circ/14\text{ mm.}$, $d^{10^\circ} 0.893$, $n_D 1.4991$, *semicarbazone*, m.p. $133\text{--}135^\circ$, *2:4-dinitrophenylhydrazone*, m.p. $83\text{--}84^\circ$. On digestion with acetic anhydride

* G.P. 149603.

† Elze, *Chem. Ztg*, 1913, **37**, 1422.

‡ *Ibid.* 1910, **34**, 85.

§ Soden and Treff, *Ber.* 1904, **37**, 1094.

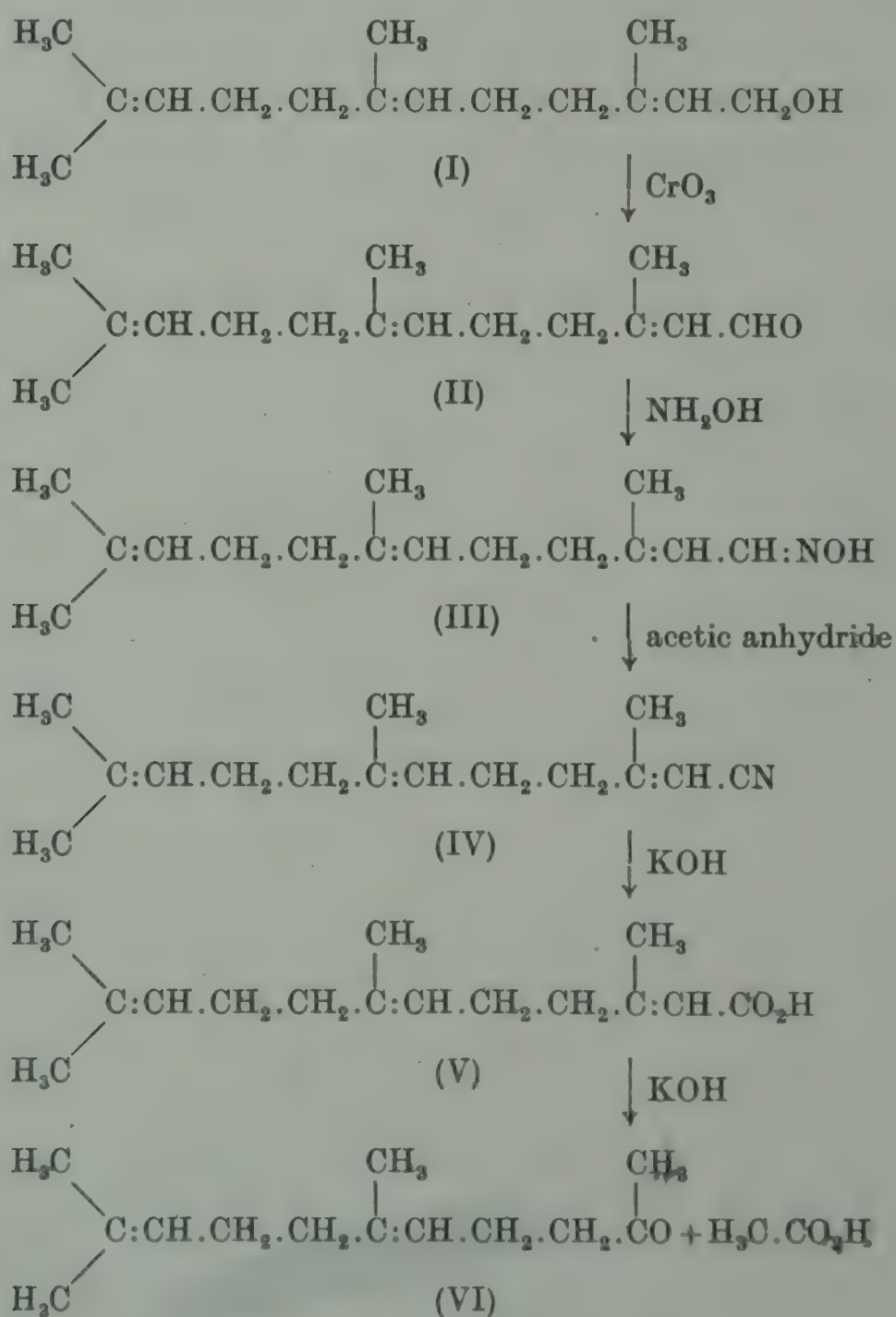
|| Schimmel's Report, 1914, April, p. 71.

¶ Elze, *Chem. Ztg*, 1910, **34**, 810.

** Naves, *Helv. Chim. Acta*, 1946, **29**, 1084; *Perf. Essent. Oil Rec.* 1947, **38**, 191; compare Igolen, *Parfums de France*, 1939, p. 80.

†† *Ber.* 1913, **46**, 1732.

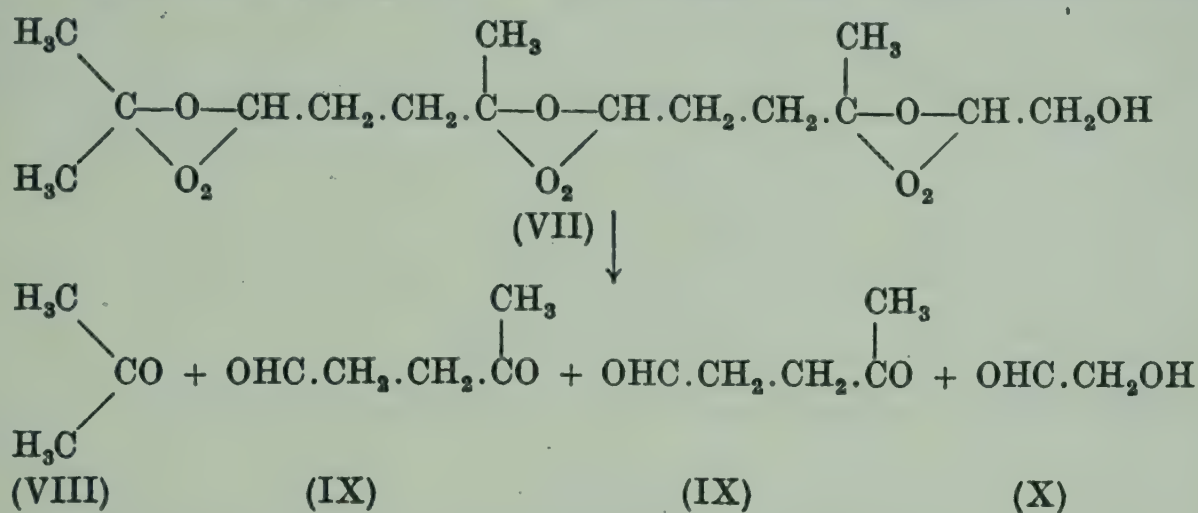
farnesaloxime yields a nitrile, the *nitrile of farnesenic acid*, which, on hydrolysis with alkali, behaves in exactly the same manner as the nitrile of geranic acid, yielding a mixture of *farnesenic acid* (V), b.p. 202–206°/16 mm., and a ketone, $C_{13}H_{22}O$. The latter is identical with $\alpha\beta$ -*dihydropseudoionone* (geranylacetone) (VI), the synthesis of which is described on p. 122 (see also Vol. I, p. 50). $\alpha\beta$ -Dihydroionone is obtained also when farnesal is digested with potassium carbonate solution.* The nitrile must therefore be represented by (IV), from which it follows that *farnesaloxime* must be (III), *farnesal* (II) and *farnesol* (I),† the reactions involved being outlined in the scheme:



* Verley, *Bull. Soc. chim.* 1924 [iv], 35, 606.

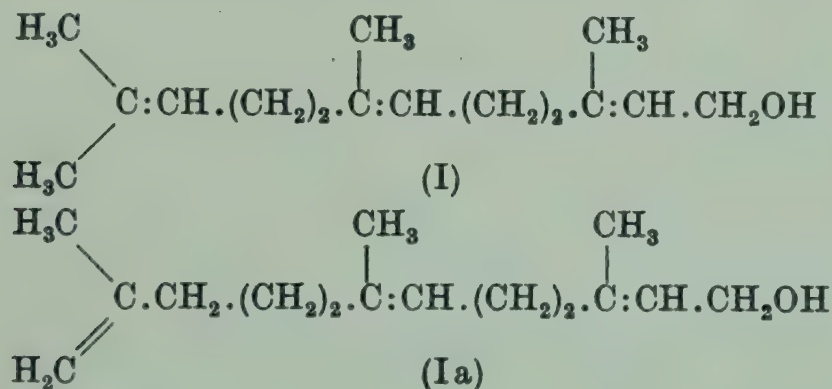
† For simplicity only one formula is used for *farnesol*.

The constitution assigned by Kerschbaum to farnesol has been confirmed by Harries and Haarmann,* who have shown that, on oxidation with ozone, a *triozonide* (VII) is obtained, which, when decomposed by water, yields acetone (VIII), levulinaldehyde (IX) and glycolaldehyde (X). Another product of the oxidation is formaldehyde and the importance of this will be discussed below. Farnesol has been synthesised by Ruzicka† who has shown that, when synthetic *dl*-nerolidol is digested with acetic anhydride, farnesol is formed (see p. 124). Although these experiments have



shown conclusively that farnesol must be represented by formula (I), yet there can be little doubt that, like geraniol and linalool (Vol. I, pp. 45, 62), it is not homogeneous, but is a mixture of the two alcohols represented by (I) and (Ia). This is supported by the observation referred to above, that formaldehyde is one of the products of ozonolysis, and also by its degradation to $\alpha\beta$ -dihydropseudoionone, which, since it is prepared from geranyl chloride, cannot be homogeneous.

In addition to farnesol being a mixture of the two structural isomerides (I) and (Ia) it is, as has been pointed out by Ruzicka,‡

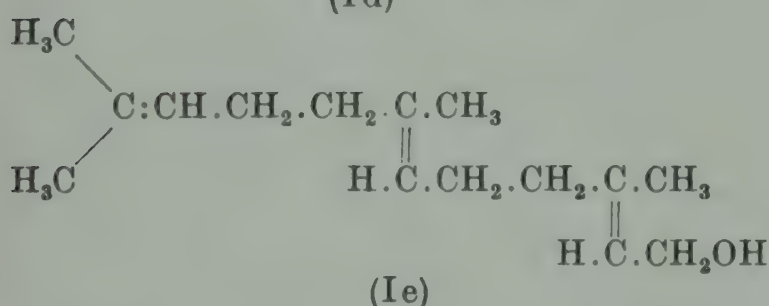
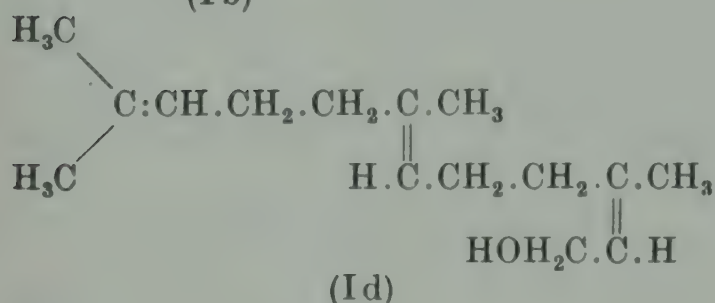
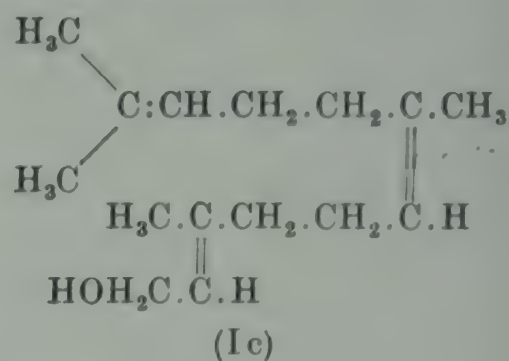
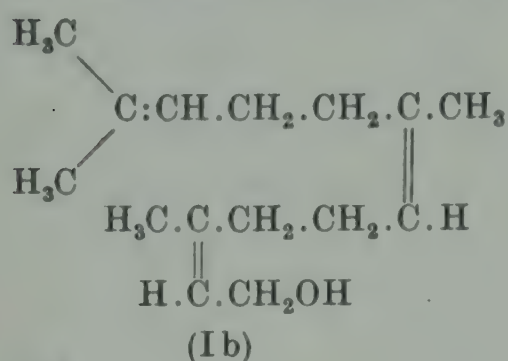


* Ber. 1913, 46, 1737.

† Helv. Chim. Acta, 1923, 6, 492 (compare Ruzicka and Firmenich, Helv. Chim. Acta, 1939, 22, 392).

‡ Ibid. 1923, 6, 495.

probably also a mixture of stereoisomerides, four modifications, (Ib), (Ic), (Id) and (Ie), being theoretically possible.*



The physical properties of farnesol, apart from its boiling-point, $120^\circ/0.3$ mm., show somewhat marked variations depending upon its origin, as will be seen from the following table:

Origin	d	n_D
Ambrette oil	$d^{18^\circ} 0.885$	1.4881
Orange oil	$d^{15^\circ} 0.8934$	$n_D^{20^\circ} 1.4899$
Citronella oil	$d^{15^\circ} 0.895$	—
Cananga oil	$d^{15^\circ} 0.895$	—
<i>dl</i> -Nerolidol	$d_4^{20^\circ} 0.8908$	$n_D^{20^\circ} 1.4890$
<i>d</i> -Nerolidol	$d_4^{18^\circ} 0.8954$	$n_D^{18^\circ} 1.4924$

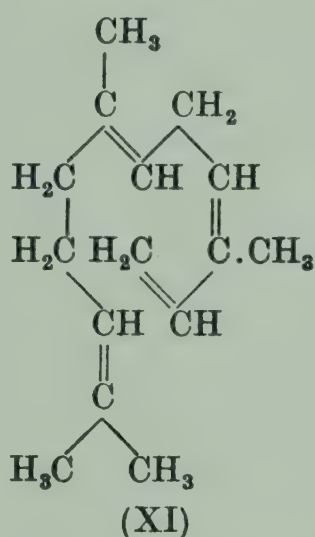
It has not proved possible to determine the configuration of farnesol, but, since linalool gives by the action of acetic anhydride a mixture of geraniol and nerol (Vol. I, p. 63), it is possible that farnesol, when prepared from nerolidol, is also a mixture of stereoisomerides, and these may differ from those present in the natural alcohol.

Farnesol, which is best purified through its hydrogen phthalate, is a colourless somewhat mobile oil, with a highly characteristic odour, which makes it valuable as a perfume.

* Farnesol may therefore be a mixture of eight isomeric alcohols.

It can be characterised by the preparation of its *di-β-naphthylurethane*, m.p. 70–70.5°,*, *3-nitrophthalate*, m.p. 93–93.5°,† *allophanate*, m.p. 79–80°,‡ and *diphenylurethane*, m.p. 54.5–55°,§ but it is usually identified by oxidation to farnesal.

On long keeping it slowly decomposes with the formation of *α-farnesene* (XI),|| which is formed also when the alcohol is digested with potassium hydrogen sulphate.¶ Farnesene** is a colourless mobile oil, b.p. 128–130°/12 mm., $d_4^{18^\circ}$ 0.8385, n_D 1.4965. It gives on ozonolysis levulinaldehyde and does not yield any naphthalene hydrocarbon on dehydrogenation with sulphur. Some further reactions of farnesene are described on p. 124.



It is possible that farnesene is identical with the acyclic sesquiterpene, b.p. 138–140°/9 mm., d^{20° 0.8489, n_D 1.5325, $[\alpha]_D + 0.36^\circ$, which Semmler and Spornitz separated from Java citronella oil.†† This hydrocarbon gave on digestion with formic acid a monocyclic terpene, b.p. 129–132°/15 mm., d^{20° 0.8892, n_D 1.5089, $[\alpha]_D + 56^\circ$, which should consist essentially of bisabolene, if the above assumption be correct, but no mention is made of the preparation of a crystalline trihydrochloride. A closely related hydrocarbon has recently been isolated by Šorm and his collaborators** from the essential oil of hops and identified as *β-farnesene* (see below).

* Späth and Vierhapper, *Ber.* 1938, **71**, 1667.

† Lennartz, *Ber.* 1943, **76**, 248.

‡ Naves, *Helv. Chim. Acta*, 1946, **29**, 1084.

§ Naves, *loc. cit.*

|| Harries and Haarmann, *Ber.* 1913, **46**, 1741.

¶ Kerschbaum, *Ber.* 1913, **46**, 1733; Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 498.

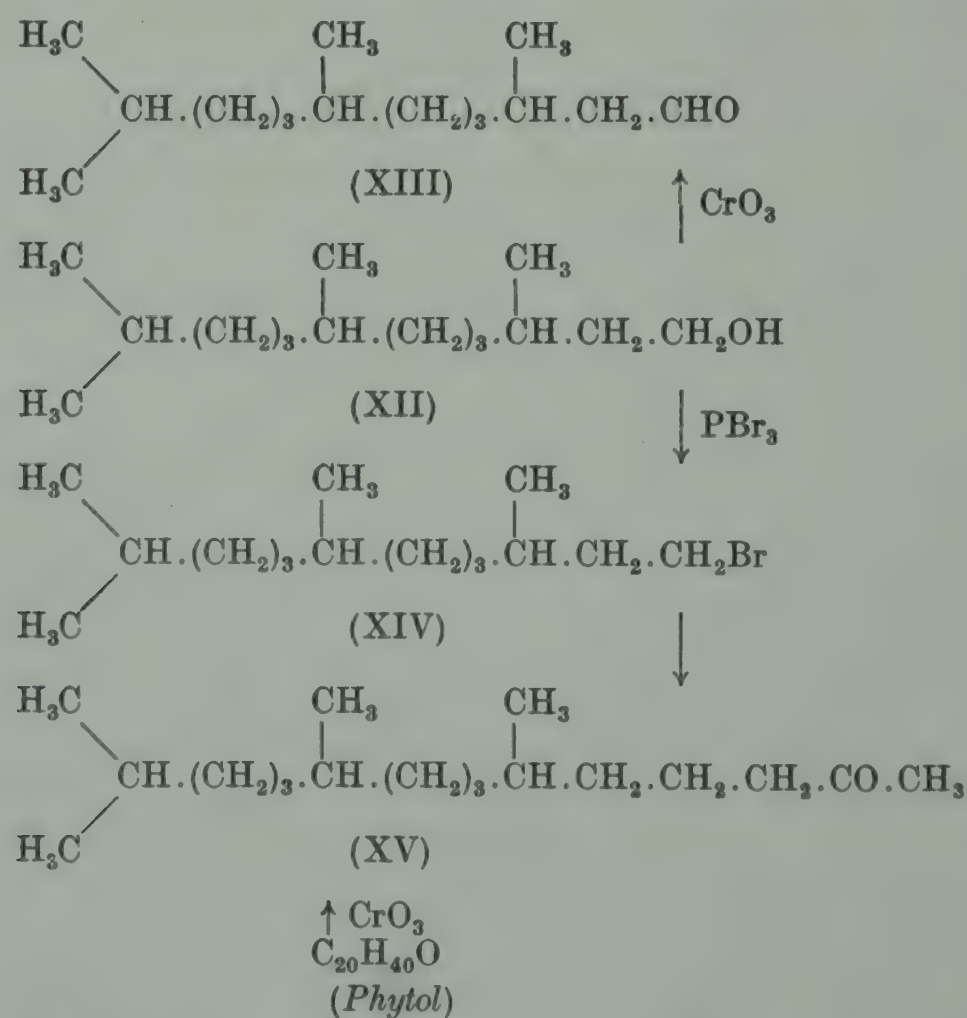
** Farnesene is obtained also by the dehydration of nerolidol (see p. 124).

†† *Ber.* 1913, **46**, 4028.

** *Coll. Czeck. Chem. Comm.* 1949, **14**, 699.

The hydrogenation of farnesol to the saturated alcohol, *hexahydrofarnesol* (XII), 2:6:10-*trimethyldodecanol*, which was first carried out by Semmler, Jonas and Roenisch,* has been investigated more recently by Fischer and Löwenberg,† who have found that the acetate of the *alcohol* is reduced more readily. Hexahydrofarnesol is a colourless oil, b.p. 151–152.5°/10 mm., $d_4^{25^\circ}$ 0.8491, $n_D^{20^\circ}$ 1.448. During the hydrogenation a considerable quantity of the saturated hydrocarbon, *farnesane*, 2:6:10-*trimethyldodecane*, b.p. 119.5–120°/11 mm., $d_4^{25^\circ}$ 0.7682, $n_D^{25^\circ}$ 1.4303, is formed. When hexahydrofarnesol is oxidised with chromic acid, it yields the saturated aldehyde *hexahydrofarnesal* (XIII), b.p. 145–147°/11 mm., *semicarbazone*, m.p. 248–250°.‡

By the action of phosphorus tribromide on hexahydrofarnesol Fischer and Löwenberg prepared the *bromide* (XIV), b.p. 150–154°/10 mm., which, on condensation with ethyl sodioacetate followed by hydrolysis, gave the *ketone*, $C_{18}H_{36}O$ (XV), b.p. 173.5–174°/10 mm., $d_4^{25^\circ}$ 0.8317, $n_D^{25^\circ}$ 1.4435, *semicarbazone*, m.p.



* *Bev.* 1917, 50, 1836.

† *Annalen*, 1928, 464, 69; *ibid.* 1929, 475, 183; compare Naves, *Helv. Chim. Acta*, 1946, 29, 1450.

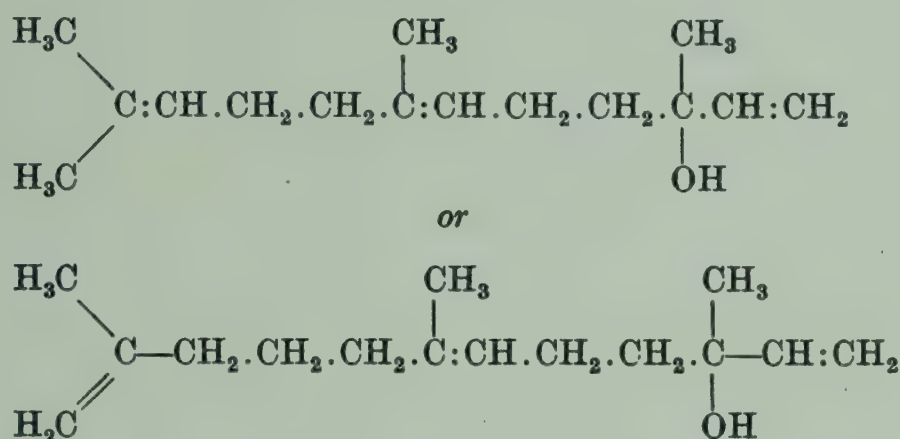
‡ v. Braun and Anton, *Ber.* 1929, 62, 1491.

66–67°, which is identical with that obtained by the oxidation of *phytol*, $C_{20}H_{40}O$, with chromic acid.

The oxidation of farnesol with potassium permanganate results in its complete degradation with the formation of acetone.*

By the action of phosphorus tribromide on farnesol Karrer and Helfenstein† have prepared *farnesyl bromide*. This could not be purified but gave on treatment with magnesium a mixture of hydrocarbons in which the presence of squalene could be detected.

NEROLIDOL



The acyclic sesquiterpene alcohol, *nerolidol*, $C_{15}H_{26}O$, was isolated by Hesse and Zeitschel‡ from neroli oil, an oil obtained from the fresh flowers of the bitter orange, *Citrus Bigaradia*. It has been shown to occur also in the essential oils present in the wood of *Myrocarpus fastigiatus*, *M. frondosus* Allem. and *Myrospermum Erythroxyllum* Allem.§ This alcohol was shown subsequently by Schimmel and Co.|| to be identical with the alcohol, *peruvicol*, which had been separated by Thoms¶ from Peru balsam.** Naves†† has recently shown that the wood of *Myroxylon Pereirae* (Royle) Klotzsch contains an essential oil the major part of which consists of nerolidol. This source may become of commercial importance.

* Kerschbaum, *Ber.* 1913, **46**, 1732.

† *Helv. Chim. Acta*, 1937, **14**, 78.

‡ *J. pr. Chem.* 1902 [ii], **66**, 504.

§ Naves, *Helv. Chim. Acta*, 1947, **30**, 275, 278.

|| *Schimmel's Report*, 1914, April, p. 75.

¶ *Arch. Pharm.* 1899, **237**, 274.

** Recently Jones and Harvey (*Proc. Roy. Soc. Queensland*, 1936, **47**, 92) have shown *melaleucol* from the essential oil of *Melaleuca viridiflora* to be identical with nerolidol.

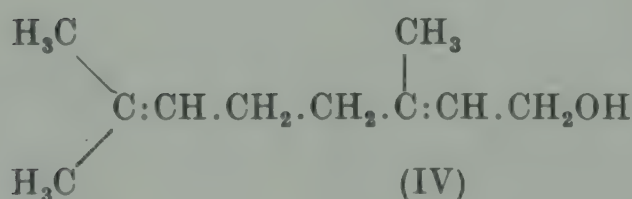
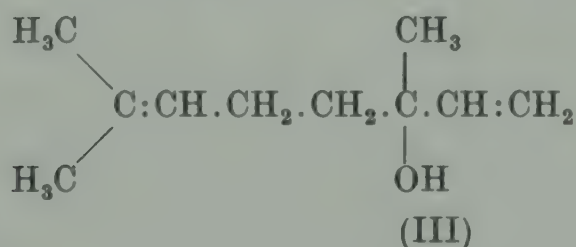
†† *Helv. Chim. Acta*, 1948, **31**, 408: cf. *Perf. Essent. Oil Rec.* 1947, **38**, 191.

Although Semmler, Jonas and Roenisch* suggested that nerolidol was probably identical with farnesol, they furnished no experimental evidence in support of their suggestion, and the investigations of Ruzicka† have shown this to be incorrect.

A consideration of the physical constants and reactions of nerolidol led Ruzicka to conclude that nerolidol bore the same relationship to farnesol as linalool (III) did to geraniol (IV). Since farnesol has been shown (p. 116) to be represented by (II), it followed, if this conclusion was correct, that nerolidol must have formula (I).‡

It was mentioned in Vol. I (p. 58) that linalool, on oxidation with chromic acid mixture, gives, like geraniol, citral, whilst, on digestion with acetic anhydride, it is converted into geraniol acetate. Ruzicka found nerolidol to behave in exactly the same manner. When it was oxidised with chromic acid mixture§ it gave the aldehyde, *farnesal* (V), corresponding to citral, whilst, when digested with acetic anhydride, the acetate of farnesol (II) was obtained together with a quantity of a hydrocarbon (see below).

Complete confirmation of the structure assigned to nerolidol was obtained by its synthesis, which followed the same lines as those adopted for the synthesis of linalool (Vol. I, p. 61). By the condensation of *geranyl chloride* (VI) with ethyl sodioacetoacetate, followed by hydrolysis with barium hydroxide, $\alpha\beta$ -*dihydropseudoionone* (geranylacetone) (VII)¶ was prepared (Vol.



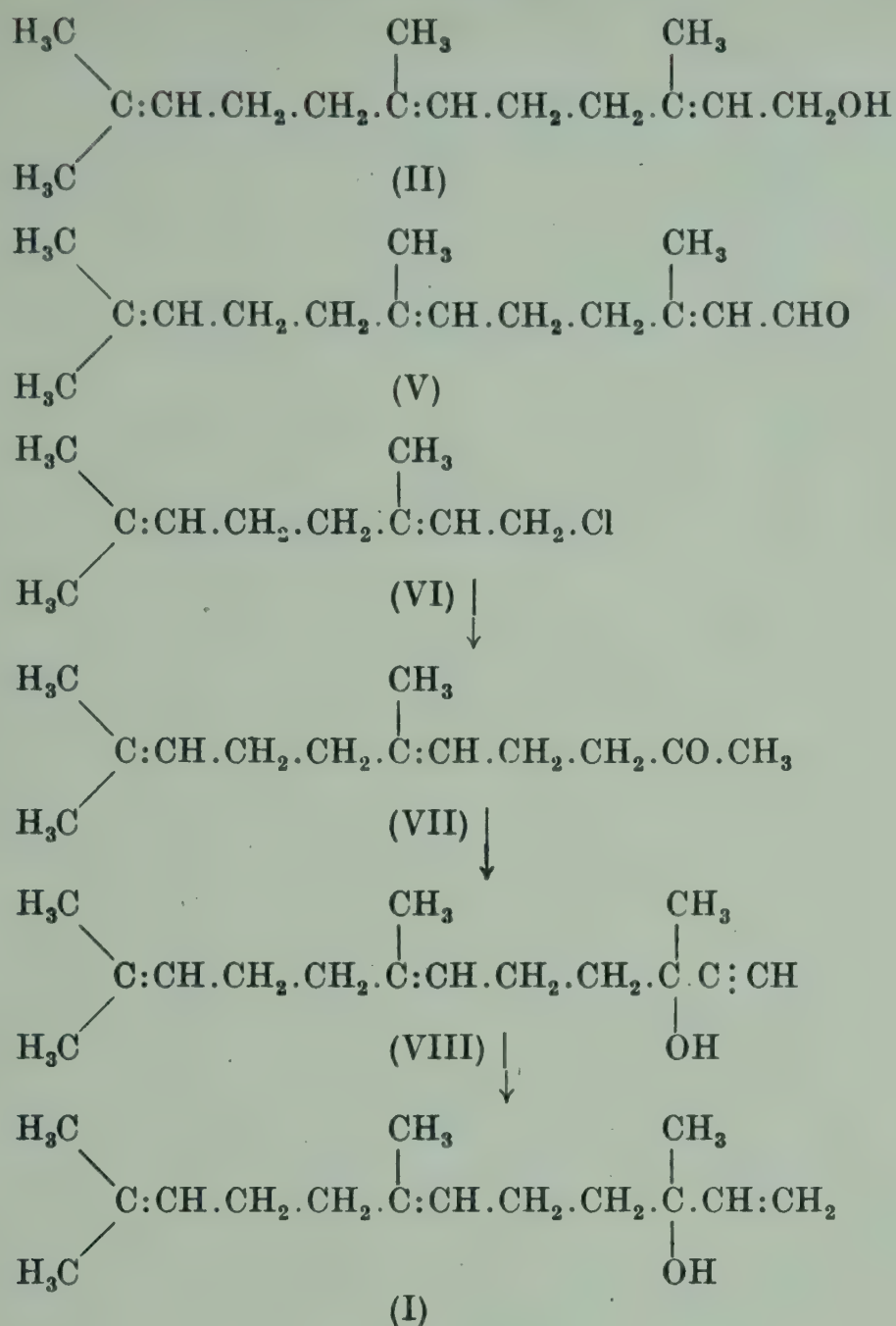
* *Ber.* 1917, 50, 1824.

† *Helv. Chim. Acta*, 1923, 6, 483, 492.

‡ It has been shown (Vol. I, pp. 45, 62) that geraniol and linalool are not homogeneous; from analogy it is probable that the same is true also of farnesol and nerolidol (compare Naves, *loc. cit.*); for simplicity only formula (I) is used.

§ Stoll and Commarmont, *Helv. Chim. Acta*, 1949, 32, 1356, 2440; Naves, *ibid.* p. 1798.

¶ Dupont and Labaune, *Sci. Inst. Rep. Roure-Bertrand Fils*, 1911, April, p. 8.

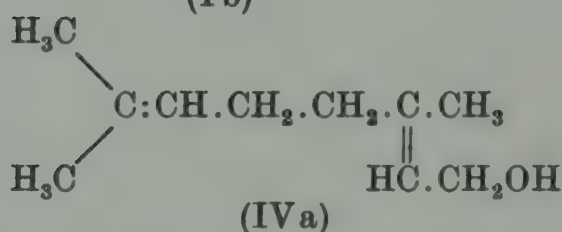
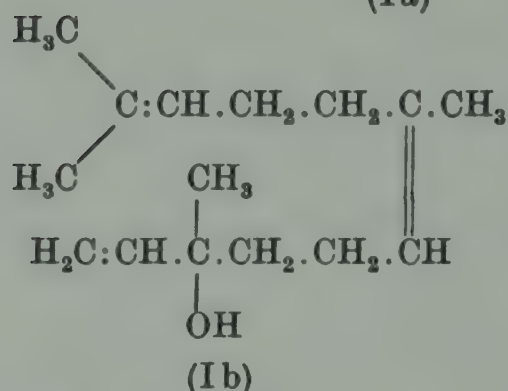
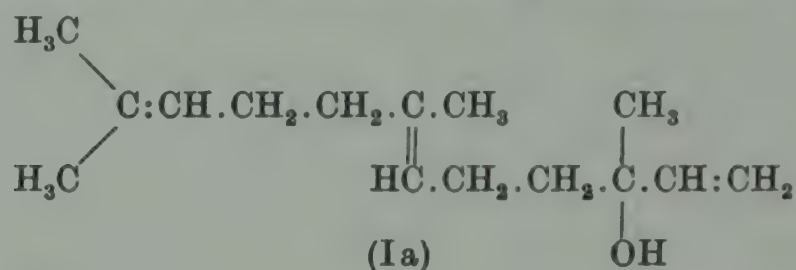


I, p. 50), which, on condensation with acetylene in the presence of sodamide, gave *homogeranylethynylmethylcarbinol* (VIII). Reduction of this acetylene alcohol with sodium in moist ethereal solution gave *dl-nerolidol* (I).

dl-Nerolidol does not give any crystalline derivatives, but the identity of the natural and synthetic alcohols was proved by the conversion of the latter into farnesol and farnesal.

d-Nerolidol, from neroli oil, is a viscid oil with a faint but pleasant odour; it boils at 125–127°/4.5 mm., $d_{15}^{15^\circ}$ 0.880, $n_D^{20^\circ}$ 1.4802, $[\alpha]_D + 12.48^\circ$, the alcohol from Peru balsam having very similar properties. For synthetic *dl*-nerolidol, Ruzicka observed the following values: b.p. 145–146°/12 mm., $d_4^{16^\circ}$ 0.8788, $n_D^{16^\circ}$ 1.4801. It has been pointed out by Ruzicka that nerolidol can exist in *cis*- and *trans*-modifications, (Ia) and (Ib). Since the

synthetic *dl*-nerolidol was prepared from geranyl chloride and geraniol has the *cis*-configuration (IV a) (Vol. I, p. 46), it may be assumed that nerolidol is represented by (Ia). No evidence has been obtained of the existence of the *trans*-modification corresponding to nerol, the physical constants of the natural alcohols from neroli oil and Peru balsam being identical.

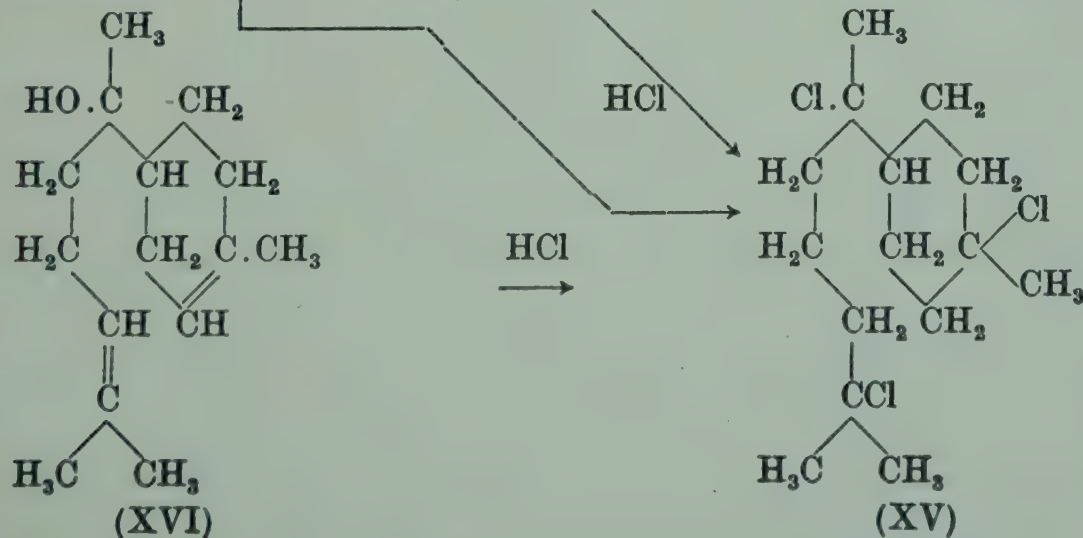
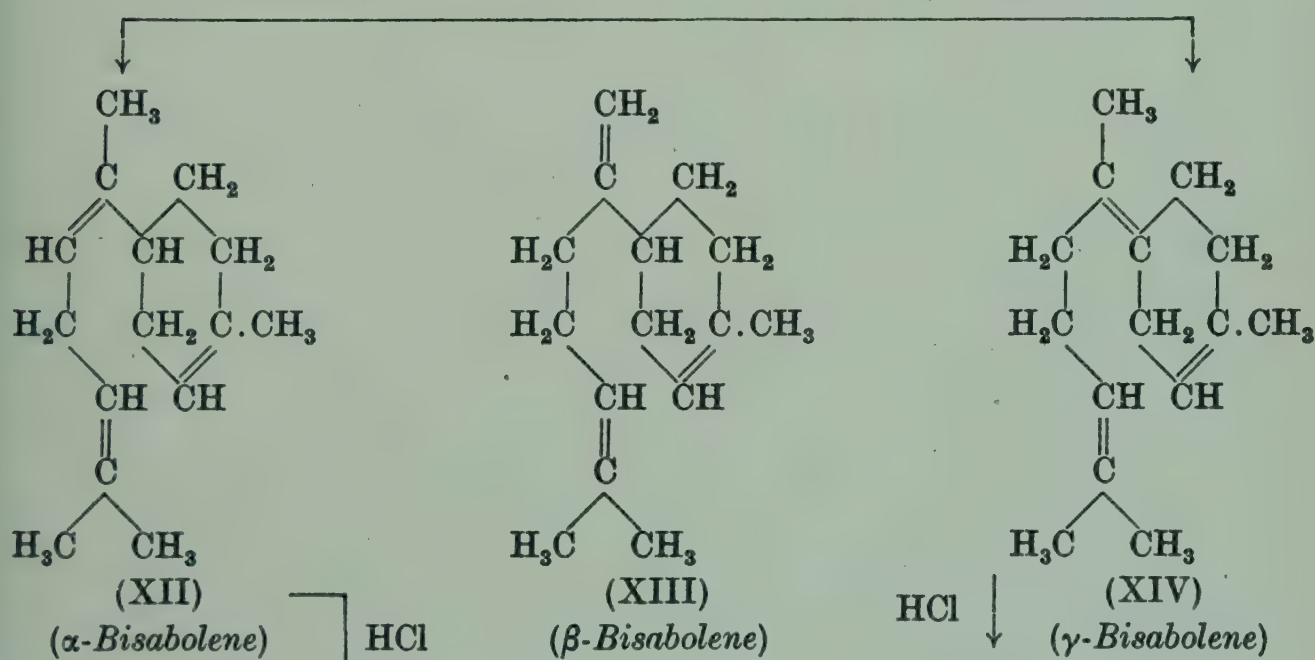
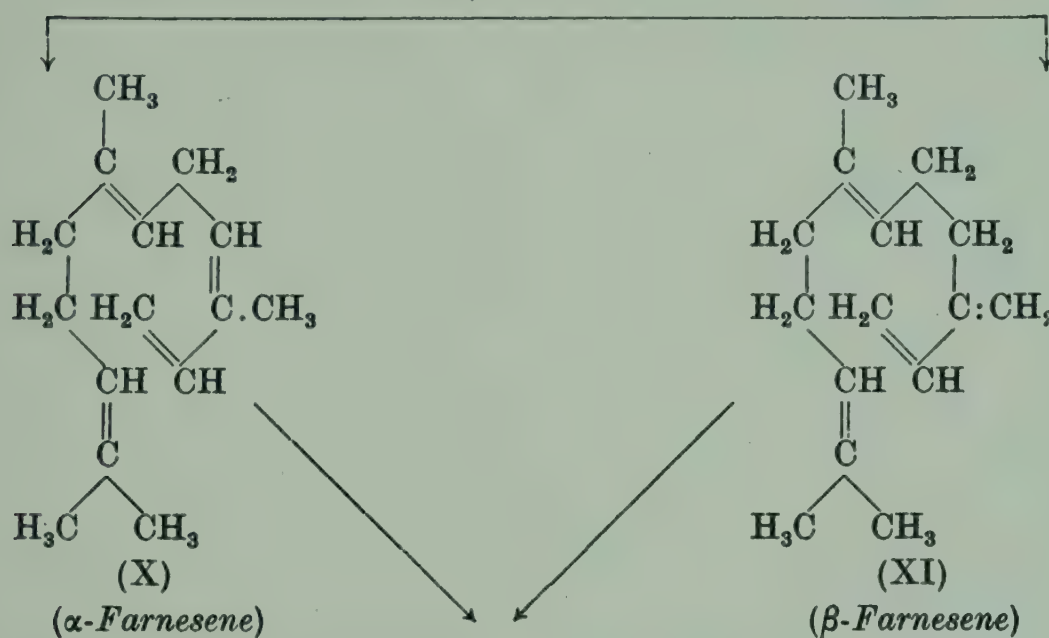
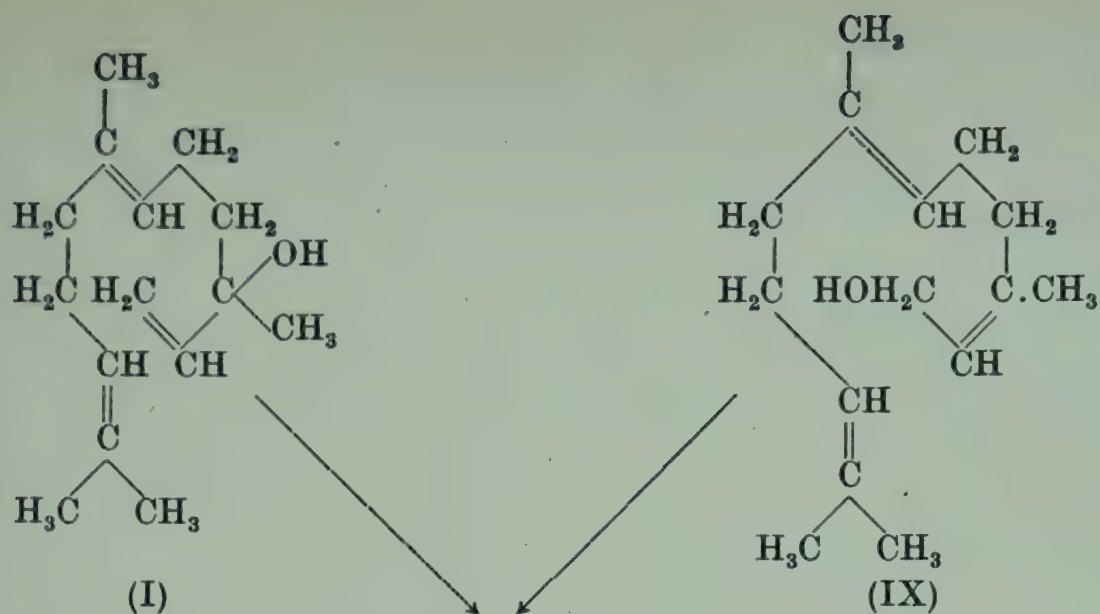


Nerolidol resembles linalool in its properties and can only be esterified with great difficulty. *dl*-Nerolidol does not yield any crystalline derivatives, but from *d*-nerolidol a *phenylurethane*, m.p. 37–38°, has been prepared.* When the alcohol is treated with hydrogen chloride in ethereal solution, it yields *farnesene tetrahydrochloride*, C₁₅H₂₈Cl₄, m.p. 50–51°.

Important results have been obtained by Ruzicka and Capato† from a study of the action of dehydrating agents on *dl*-nerolidol. It was mentioned above that when the alcohol was digested with acetic anhydride, in addition to farnesol, a hydrocarbon was obtained. This acyclic hydrocarbon, which is formed also by the dehydration of farnesol (IX) with potassium hydrogen sulphate, is probably a mixture of the two hydrocarbons represented by (X) and (XI), which may be designated α - and β -farnesenes. If

* Schimmel's Report, 1914, April, p. 76; compare Spoelstra, *Rec. trav. chim.* 1931, 50, 433.

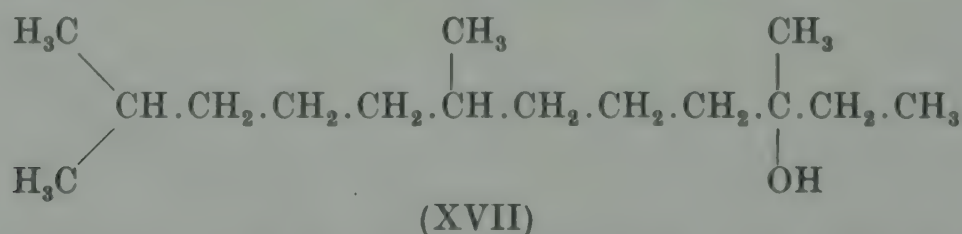
† *Helv. Chim. Acta*, 1925, 8, 259.



farnesene is digested for a short time with formic acid, it yields a monocyclic sesquiterpene, which, from its method of preparation, may obviously be represented by either (XII), (XIII) or (XIV). The reaction as formulated corresponds to the conversion of linalool into dipentene and terpinolene. This monocyclic terpene, b.p. 125–127°/12 mm., $d_4^{18^\circ}$ 0.8451, $n_D^{18^\circ}$ 1.4823, gave with hydrogen chloride a crystalline *trihydrochloride*, m.p. 79–80°, identical with *bisabolene trihydrochloride* (XV), and from this, by the action of sodium acetate in acetic acid solution, bisabolene, identical with the natural sesquiterpene (p. 9), was prepared. The three hydrocarbons (XII), (XIII) and (XIV) may be designated α -, β - and γ -bisabolenes; as was shown on p. 10 both the natural and synthetic hydrocarbons consist essentially of γ -bisabolene (XIV).

In addition to the hydrocarbons, farnesene and bisabolene, nerolidol (and farnesol) give on treatment with formic acid or acetic-sulphuric acid the formate (or acetate) of a sesquiterpene alcohol. The alcohol, obtained on hydrolysis, was freed from farnesol by treatment with phthalic anhydride and consisted of nearly pure *bisabolol* (XVI), b.p. 154–156°/12 mm., $d_4^{18^\circ}$ 0.9216, $n_D^{17^\circ}$ 1.4939.* On treatment with hydrogen chloride, bisabolene trihydrochloride (XV) was obtained. It is of interest that French lavender oil contains bisabolol,† its presence being inferred by the isolation of bisabolene trihydrochloride when the tertiary sesquiterpene alcohol fraction of the oil was treated with hydrogen chloride.

On catalytic hydrogenation nerolidol behaves in a similar manner to farnesol (see p. 120) affording a mixture of *farnesane*, 2:6:10-*trimethyldodecane* and *hexahydronerolidol* (XVII), $C_{15}H_{32}O$, b.p. 117°/1.8 mm., $d_4^{20^\circ}$ 0.8319, $n_D^{20^\circ}$ 1.4467.‡



* Compare Ruzicka and Liguori, *Helv. Chim. Acta*, 1932, 15, 3.

† Seidel, Müller and Schinz, *Helv. Chim. Acta*, 1944, 27, 738.

‡ Naves, *Helv. Chim. Acta*, 1946, 29, 1450.

B. MONOCYCLIC ALCOHOLS

ELEMOL

In 1907 Clover* separated from Manila oil of elemi, which is obtained from the oleo-resin of *Canarium luzonicum* A. Gray, a crystalline alcohol, *elemol*, $C_{15}H_{26}O$. Elemi oil contains, in addition to elemol, elemicin, and, since the two substances boil at the same temperature, Semmler and Futung Liao† purified elemol through its benzoate. The alcohol obtained from this on hydrolysis was an oil, b.p. $152-156^{\circ}/17$ mm., $d^{20^{\circ}} 0.9411$, $n_D 1.503$, $\alpha_D -5^{\circ}$, which from its physical constants, $[R_L]_D 69.73$, $C_{15}H_{26}O$, $\epsilon_2 = 69.77$, was apparently monocyclic and contained two ethylenic linkages. It could not be reduced by sodium and alcohol, but on catalytic hydrogenation in the presence of platinum, *tetrahydroelemol*, $C_{15}H_{30}O$, m.p. 35.5° , b.p. $138-142^{\circ}/13$ mm., $d^{20^{\circ}} 0.9080$, $n_D 1.4807$, $\alpha_D -2^{\circ}$, was prepared. Somewhat different constants, m.p. $59-61^{\circ}$, $d^{55^{\circ}} 0.8903$, have been recorded‡ for a tetrahydroelemol which has been purified through its *p*-nitrobenzoate, m.p. $62-64^{\circ}$, $[\alpha]_D +12.0^{\circ}$ (in benzene), $+9.3^{\circ}$ (in chloroform) or through its 3:5-dinitrobenzoate, m.p. $127-129^{\circ}$, $[\alpha]_D +11.6^{\circ}$ (in benzene), $+6.3^{\circ}$ (in chloroform). This saturated alcohol, on dehydration with formic acid, gave the hydrocarbon, *tetrahydroelemene*, $C_{15}H_{28}$, b.p. $118-120^{\circ}/12$ mm., $d^{20^{\circ}} 0.8576$, $n_D 1.4760$, $\alpha_D -15.2^{\circ}$. By the dehydration of elemol, the sesquiterpene, *elemene*, $C_{15}H_{24}$, b.p. $115-117^{\circ}/10$ mm., $d^{20^{\circ}} 0.8797$, $n_D 1.4971$, was obtained, which gave, on catalytic hydrogenation, *hexahydroelemene*, $C_{15}H_{30}$, b.p. $114-116^{\circ}/10$ mm., $d^{20^{\circ}} 0.8450$, $n_D 1.4621$, $[\alpha]_D -4.8^{\circ}$. In order to gain an insight into the structure of elemol, Semmler and Futung Liao oxidised tetrahydroelemene with ozone but, before proceeding to discuss their results, it is necessary to refer to a later investigation due to Jansch and Fantl.§ These authors, by alternate distillation and draining on porous porcelain, succeeded in purifying elemol, which they obtained as a crystalline solid, m.p. 46° , differing somewhat in its physical properties from the alcohol described

* *Philippine J. Sci.* 1907, 2, A 1.

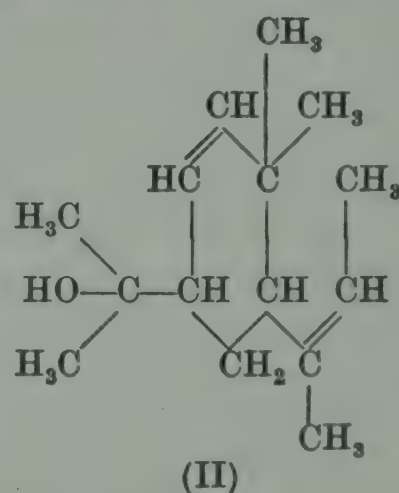
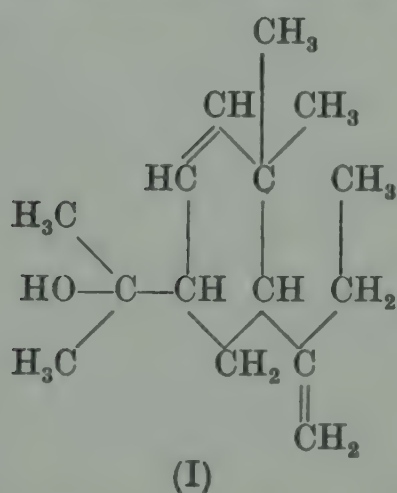
† *Ber.* 1916, 49, 794; 1917, 50, 1286.

‡ *Schimmel's Report*, 1940, p. 46.

§ *Ibid.* 1923, 56, 1363.

by Semmler and Futung Liao. Jansch and Fantl suggested that crystalline elemol, which they termed α -elemol, was a dicyclic alcohol, whereas Semmler and Futung Liao's liquid alcohol was monocyclic, ring fission occurring during the process of purification. Ruzicka and Pfeiffer,* who were simultaneously engaged in the investigation of elemol, showed Jansch and Fantl's assumption to be incorrect. If elemol benzoate is purified by distillation at a pressure of 0.25 mm., then, on hydrolysis, it yields a crystalline alcohol, identical with that described by Jansch and Fantl. It is, however, possible that, if the distillation be carried out at a somewhat higher pressure (10 mm.) some molecular rearrangement does occur, but there can be no doubt that both the liquid and crystalline alcohols are monocyclic and contain two ethylenic linkages.

Very great difficulties have been encountered in determining the constitution of elemol, but, as the outcome of a prolonged investigation by Ruzicka and Pfeiffer and Ruzicka and van Veen,[†] there can be little doubt that it consists essentially of the alcohol represented by (I). It is possible that it may also contain a small quantity of the alcohol (II). Elemol is undoubtedly a



tertiary alcohol, since it does not react with phthalic anhydride, is readily dehydrated to the hydrocarbon, elemene, and when heated with zinc dust at 220° under pressure yields *elemene*, $C_{15}H_{26}$, b.p. 115–119°/10 mm., d_4^{17} 0.8830, n_D^{17} 1.4950.[‡]

When elemol is dehydrogenated with selenium it yields eudalene, some vetivazulene (see p. 7) being also formed.[§] From analogy with selinene, it is probably therefore an alcohol having

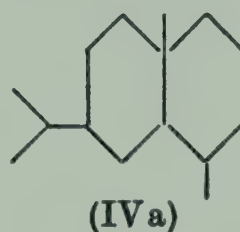
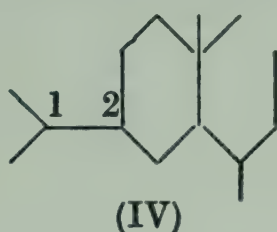
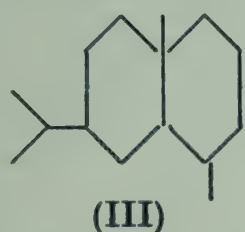
* *Helv. Chim. Acta*, 1926, **9**, 841.

† *Annalen*, 1929, **476**, 70.

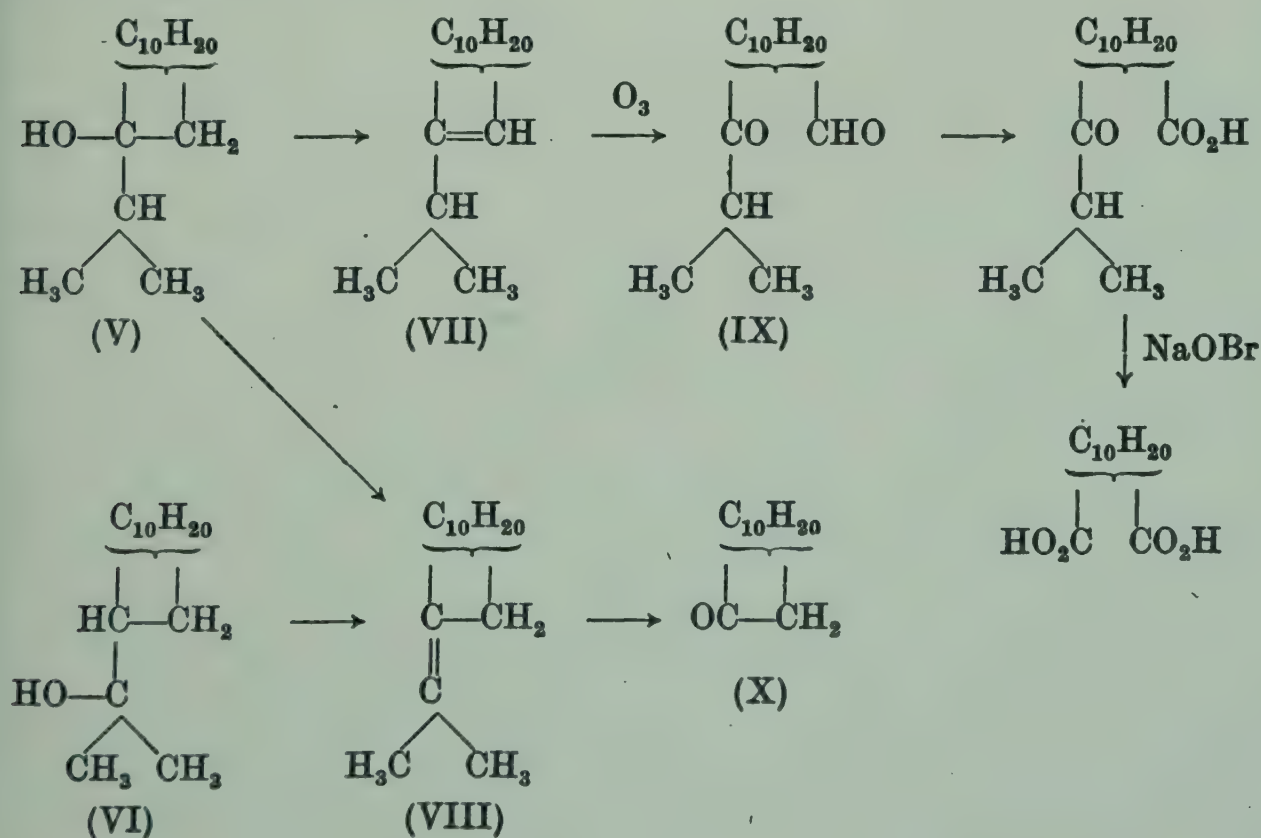
‡ Jansch and Fantl, *loc. cit.* p. 1368.

§ Sørensen and Hougen, *Acta Chem. Scand.* 1948, **2**, 447.

the carbon skeleton (III) and, since there is no doubt that the isopropyl group is present in a ring, it may be represented by one of the skeleton formulae (IV) and (IV a).



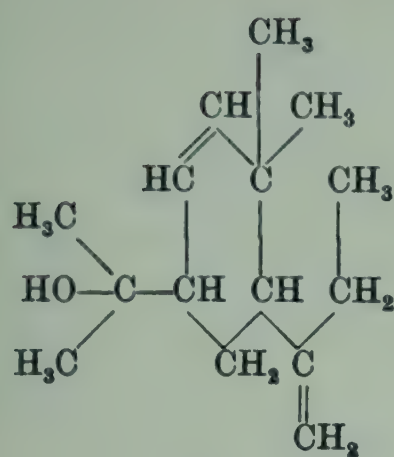
It was readily shown that the hydroxyl group must be situated in either position 1 or 2 in formula (IV). By the oxidation of tetrahydroelemene with ozone, Semmler and Futung Liao had obtained a *ketonic aldehyde*, $C_{15}H_{28}O_2$, which could be further oxidised to a *ketonic acid*, $C_{15}H_{28}O_3$, and this gave on treatment with sodium hypobromite a *dicarboxylic acid*, $C_{12}H_{22}O_4$. Whilst Ruzicka and Pfeiffer were able to confirm these results, they found that, in addition to the ketonic aldehyde, a *ketone*, $C_{12}H_{22}O$, *semicarbazone*, m.p. 169° , was formed. The separation of this substance showed that tetrahydroelemene was not homogeneous, and that it must be a mixture of the two hydrocarbons represented by (VII) and (VIII), derived from an alcohol having the structure (V) or (VI). The ketonic aldehyde (IX) and its oxidation products would then be formed from (VII) and the ketone (X) from (VIII).



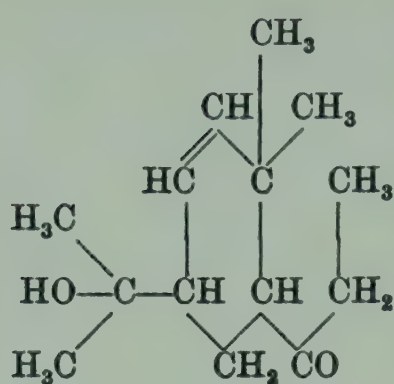
Direct proof of the position of the hydroxyl group has not been obtained, but there can be little doubt that it is in the position 1 in formula (IV). Semmler and Futung Liao found that elemol could be benzoylated by benzoyl chloride in pyridine solution; a comparative study of the reactivity of 4-hydroxy-*p*-menthane and of 8-hydroxy-*p*-menthane showed that, whereas the latter could be benzoylated quite readily under these conditions, the former could not. It follows therefore that elemol must be similarly constituted to 8-hydroxy-*p*-menthane.

The position of one of the ethylenic linkages in elemol was readily determined. On ozonolysis the alcohol yields a mixture of mono- and di-ozonides, the former of which, on decomposition in the usual manner, gives a *ketonic alcohol*, $C_{14}H_{24}O_2$, b.p. 125–135°/0.3 mm. The formation of this substance leaves no doubt that one of the ethylenic linkages must be exocyclic and, with the skeleton (IV) as the basis, elemol can be represented by either (XI), (XII), (XIII) or (XIV), when the ketonic alcohol obtained on ozonolysis would be either (XV), (XVI), (XVII), or (XVIII). Elemol does not contain a conjugated system of ethylenic linkages, since it cannot be reduced with sodium in either ethyl or amyl alcoholic solution, nor does it react with ethyl diazoacetate. Formula (XII) can therefore be eliminated. The ketonic alcohol, on digestion with formic acid, is dehydrated and yields an unsaturated *ketone*, $C_{14}H_{22}O$, b.p. 125–127°/12 mm., which contains two ethylenic linkages. When this ketone is reduced with sodium in alcoholic solution only the carbonyl group is attacked with the formation of an unsaturated *alcohol*, $C_{14}H_{24}O$, b.p. 119–122°/12 mm. The ethylenic linkages in the ketone cannot therefore be conjugated, which must be the case if it is formed by the dehydration of either (XVI), (XVII) or (XVIII). It follows, therefore, that the unsaturated ketonic alcohol must be (XV) and elemol itself (XI). The unsaturated ketone is probably represented by (XIX) and it yields on catalytic hydrogenation the saturated *ketone* (XX), b.p. 131–133°/18 mm., $d_4^{15^\circ}$ 0.9120, $n_D^{15^\circ}$ 1.4702, *semicarbazone*, m.p. 172°.

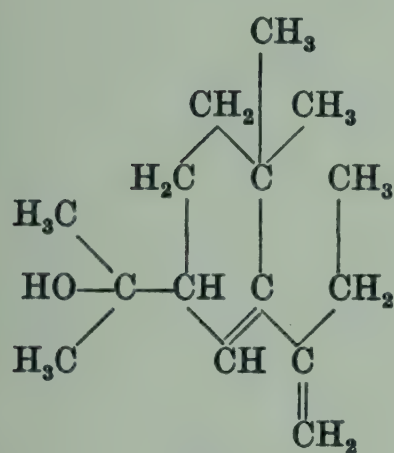
Further indirect evidence of the position of the second ethylenic linkage was obtained by the ozonolysis of elemene. Although this hydrocarbon is undoubtedly a mixture, it always yields acetone on oxidation, the formation of which can only be



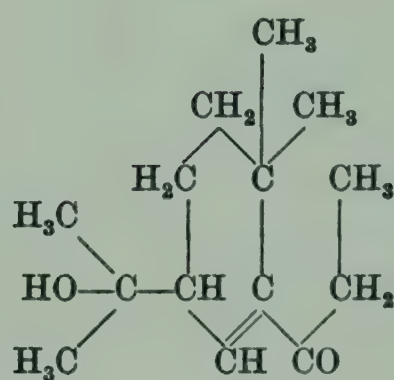
(XI)



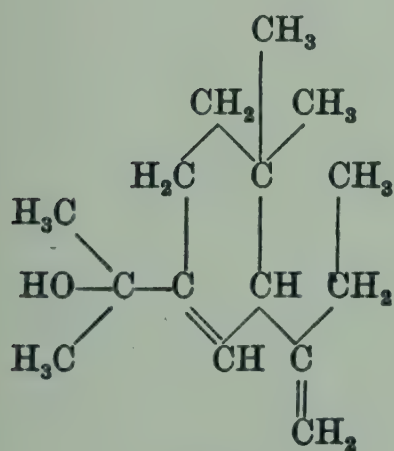
(XV)



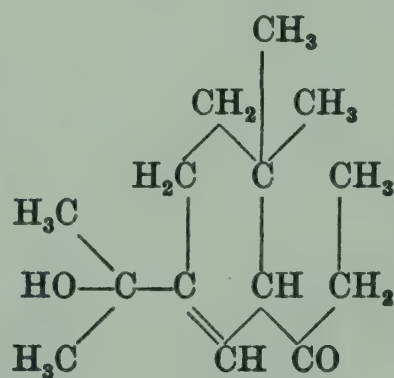
(XII)



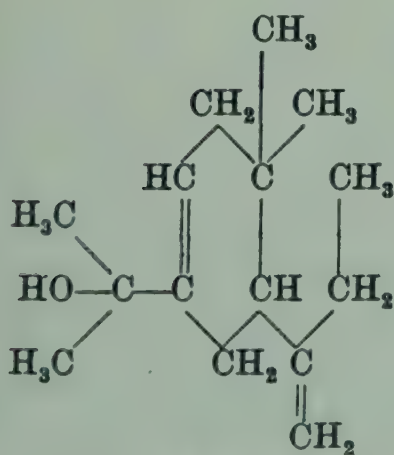
(XVI)



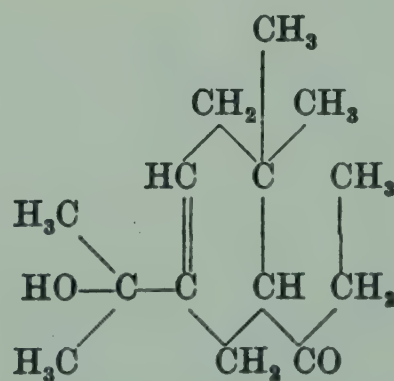
(XIII)



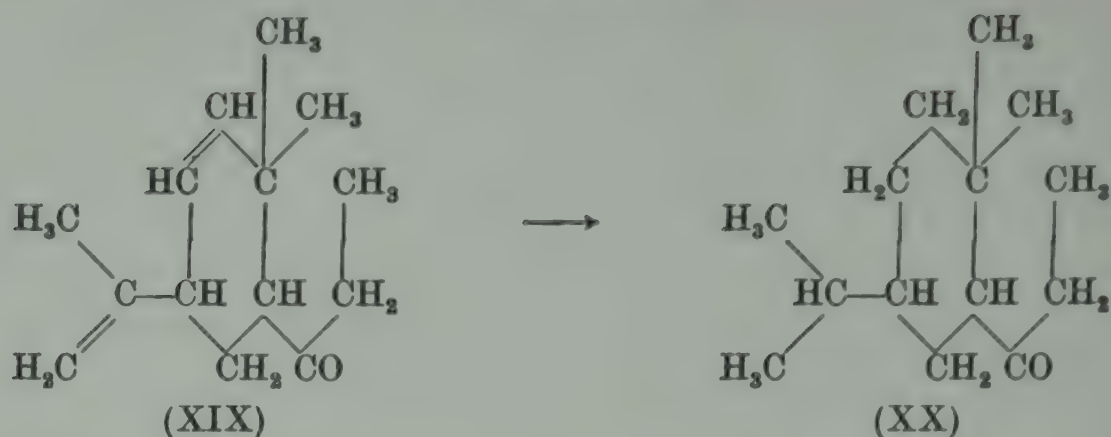
(XVII)



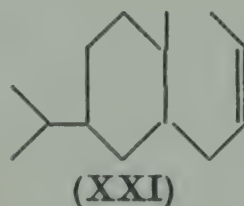
(XIV)



(XVIII)



accounted for if the alcohol from which it is derived is represented by either (XI) or (XII). The reasons for rejecting (XII) have been given already, so that (XI) may be regarded with some degree of certainty as correctly representing elemol. There is, however, some evidence that it is not quite homogeneous. On oxidation with ozone in addition to the ketonic alcohol (XV), some acetaldehyde* and an *acid*, m.p. 145° , having the composition $C_{13}H_{24}O_3$, are obtained. This acid can be readily converted into a *lactone*, $C_{13}H_{22}O_2$, m.p. 37° . It is obtained also by the oxidation of dihydroelemol (see below). Ruzicka and van Veen suggest tentatively that it is derived from an elemol having the carbon skeleton (XXI), but direct proof of this is not available.



Elemol, when purified through the crystalline *phenylurethane*, m.p. $112-113^{\circ}$,[†] melts at $51-52^{\circ}$, b.p. $144-145^{\circ}/15\text{ mm.}$, $d_4^{15^{\circ}} 0.9400$, $n_D^{15^{\circ}} 1.5042$. Apart from the somewhat higher melting-point, the constants of the alcohol purified in this manner differ little from those of that purified through the benzoate.

Elemol can also be conveniently isolated from essential oils by the preparation of its *p*-nitrobenzoate, m.p. $74-76^{\circ}$, $[\alpha]_D -2.8^{\circ}$ (in benzene), -7.82° (in chloroform) or its 3:5-dinitrobenzoate, m.p. $122-123^{\circ}$, $[\alpha]_D \pm 0^{\circ}$ (in benzene), -10.0° (in chloroform).[‡] Elemol obtained by hydrolysis of these substituted benzoates had m.p. 52° , b.p. $133^{\circ}/6\text{ mm.}$, $d_{15}^{55^{\circ}} 0.9222$, $[\alpha]_D -9.59^{\circ}$ (in

* This is probably formed from an alcohol having the structure (II) (p. 128).

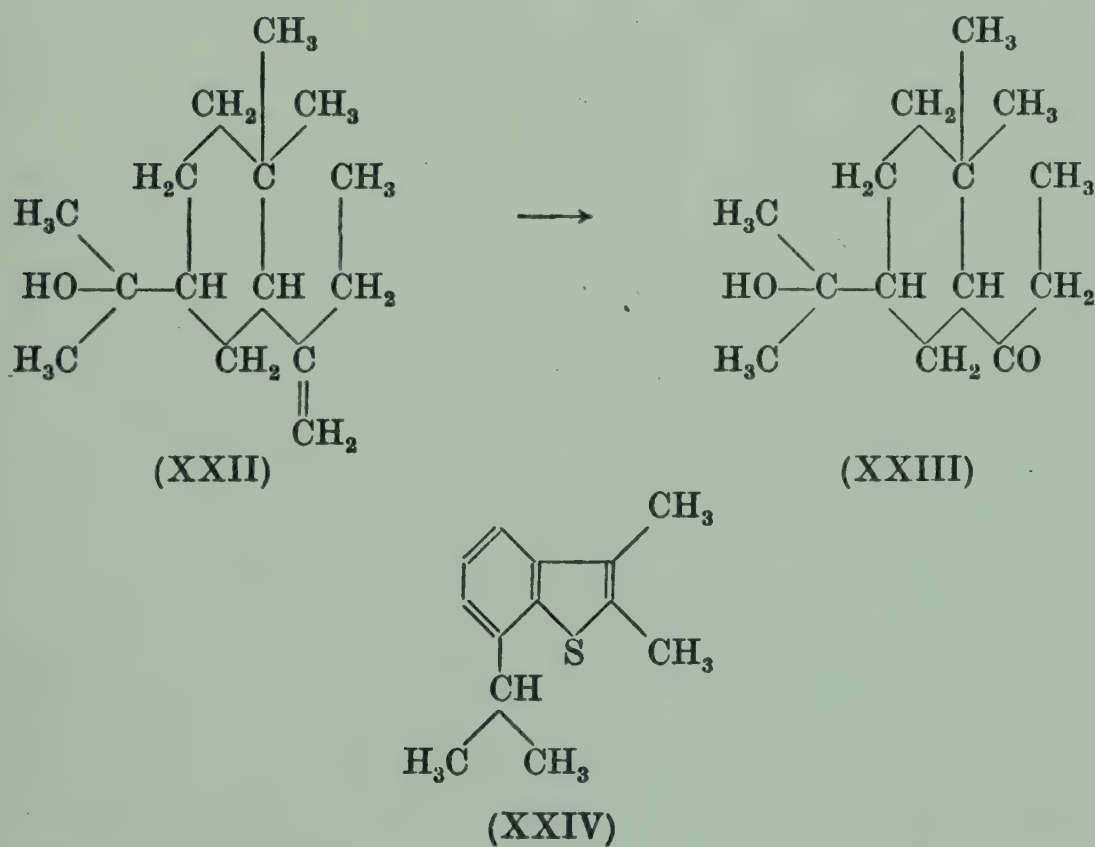
† Glichitch, *Parfums de France*, 1926, p. 256.

‡ Schimmel's Report, 1940, p. 46.

benzene), -4.35° (in chloroform) in good agreement with the physical constants already recorded.

Although elemol, when purified through its benzoyl derivative, can be readily reduced to tetrahydroelemol, the alcohol, which has only been purified by distillation, is hydrogenated with much greater difficulty and yields *dihydroelemol*, m.p. 49° , b.p. $138^{\circ}/12$ mm., $d_4^{15^{\circ}}$ 0.934, $n_D^{15^{\circ}}$ 1.4925, best isolated as its *p*-nitrobenzoate, m.p. $84-86^{\circ}$, $[\alpha]_D + 7.0^{\circ}$ (in benzene), $\pm 0^{\circ}$ (in chloroform), or 3:5-dinitrobenzoate, m.p. $95-97^{\circ}$, $[\alpha]_D + 4.6^{\circ}$ (in benzene), $+ 1.66^{\circ}$ (in chloroform). Dihydroelemol also forms a characteristic *naphthylurethane*, m.p. 108° . This alcohol must be represented by (XXII), since, on oxidation, it gives the ketone (XXIII), identical with that prepared from the unsaturated ketone (XV) (p. 131).

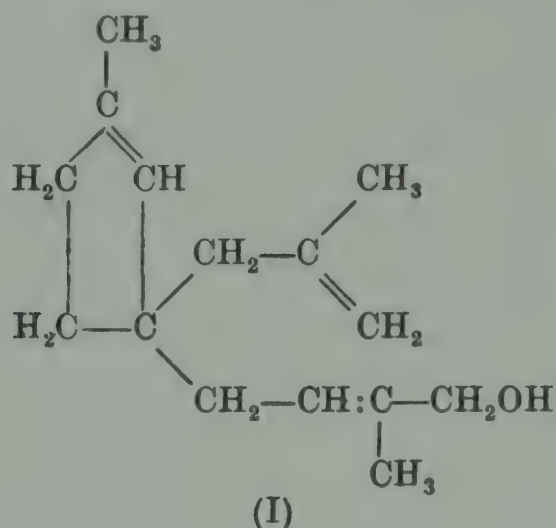
On treatment with formic acid, dihydroelemol, like elemol and tetrahydroelemol, readily lost water to furnish *dihydroelemene*, b.p. 112–114°/8 mm., d^{20}_D 0.8785, n^{20}_D 1.4741, $[\alpha]_D -8^\circ$.



It has been mentioned that elemol on dehydrogenation with selenium gives eudalene, but if sulphur is used then, in addition to this hydrocarbon, a *thionaphthene* derivative, $C_{14}H_{18}S$, is obtained, the *picrate* of which melts at 110–111°. For this substance Ruzicka and van Veen suggest the structure (XXIV).

LANCEOL

The alcohol, *lanceol*, $C_{15}H_{24}O$, was isolated by Penfold* from the essential oil present in the wood of *Santalum lanceolatum* and was subsequently investigated by Bradfield, Francis, Penfold and Simonsen.† These authors tentatively suggested that the alcohol is best represented by (I).‡



Lanceol is a primary alcohol since it yields on oxidation with chromic acid an *aldehyde*, $C_{15}H_{22}O$, b.p. $165-175^{\circ}/15$ mm., *semi-carbazone*, m.p. $151-152^{\circ}$, *p-nitrophenylhydrazone*, m.p. $135-136^{\circ}$. It is monocyclic since on treatment with percamphoric acid it shows oxygen absorption equivalent to three ethylenic linkages which cannot be conjugated, since the alcohol is not reduced by sodium and alcohol nor does it react with α -naphthoquinone.

On ozonolysis lanceol gave, amongst other unidentified products, formaldehyde, hydroxyacetone, levulinic acid and a monoethylenic *keto-dicarboxylic acid*, m.p. 174° (*di-p-phenacyl ester*, m.p. $105-106^{\circ}$), subsequently shown by Owen§ to possess the formula $C_{11}H_{14}O_5$. On further oxidation of this acid with ozone, δ -acetylbutane- $\alpha:\beta$ -dicarboxylic acid (II) was obtained. The keto-dicarboxylic acid showed absorption in the ultra-violet characteristic of an $\alpha:\beta$ -unsaturated ketone. On the basis of these facts it must be represented by one of the formulae (III)–(VIII).|| It is unlikely that this keto-acid is a primary product of the ozonolysis and it is very probably formed from a diketonic precursor by an internal aldol-type condensation, e.g. (III)

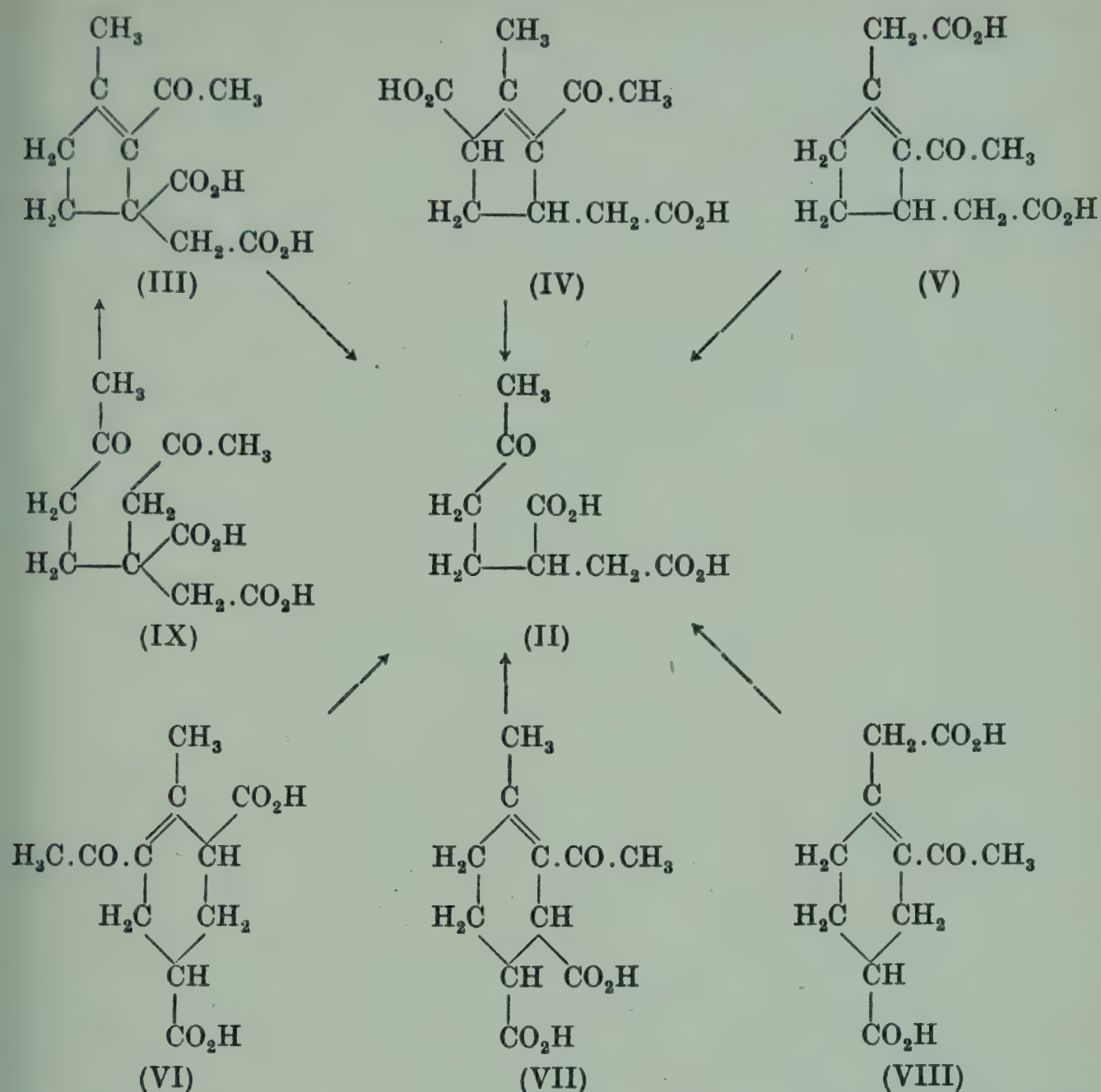
* *J. Proc. Roy. Soc. New South Wales*, 1928, 62, 60; 1932, 66, 240.

† *J.C.S.* 1936, p. 1619.

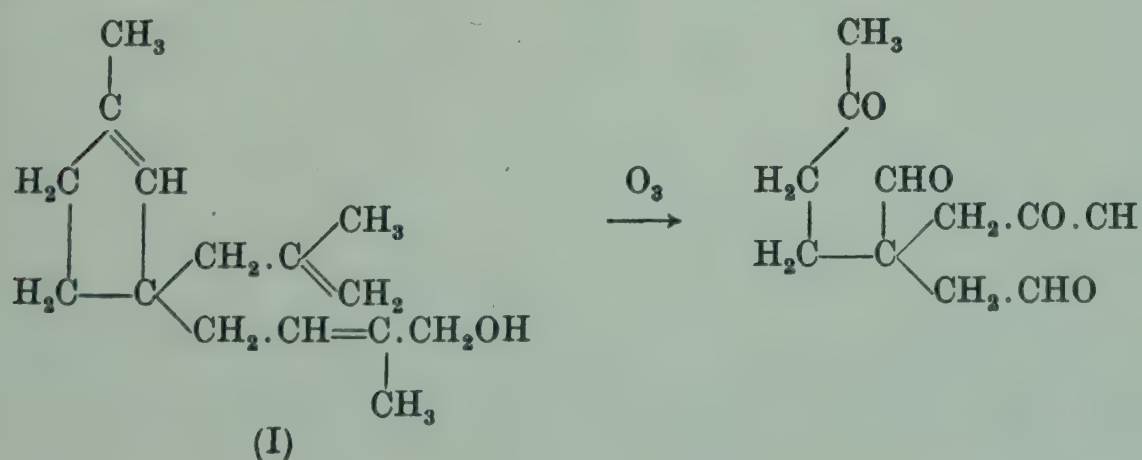
‡ Birch (private communication) has shown that lanceol is the allylic alcohol, 14-hydroxy- β -bisabolene.

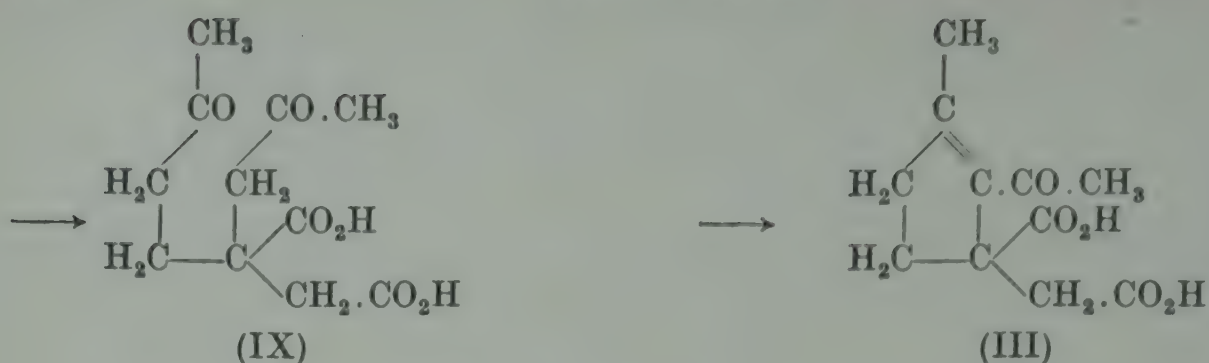
§ *J.C.S.* 1949, p. 1582.

|| Owen, *loc. cit.*



would be formed from (IX) and so on. Formulae (IV), (V), (VI) and (VIII) would require β -ketonic acids as precursors and therefore are less likely than (III) and (VII). Of the latter spectroscopic evidence favoured (III) rather than (VII) in agreement with the formula (I) for lanceol. The degradation of lanceol on ozonolysis may then be represented as follows:





Lanceol is a viscid colourless oil, b.p. 175–176°/17 mm., $d_{15}^{15^\circ}$ 0.9474, $n_D^{25^\circ}$ 1.5074, $[\alpha]_{5461} - 77.4^\circ$, $[\alpha]_{5780} - 67.8^\circ$, with a faint odour reminiscent of santalol. It can best be characterised by its *allophanate*, m.p. 114–115°, or by the preparation of the *strychnine* salt, m.p. 103–104°, of the hydrogen phthalate.

C. DICYCLIC ALCOHOLS

CADINOL

In 1914 Semmler and Jonas* isolated from galbanum oil (from *Peucedanum galbanifluum* Baill. and *P. rubricaula* Baill.) a dextrorotatory sesquiterpene alcohol, *d-cadinol*, $\text{C}_{15}\text{H}_{26}\text{O}$, which gave cadinene dihydrochloride on treatment with hydrogen chloride. Later Henderson and Robertson† separated the optical enantiomorph, *l-cadinol*, from oil of cubebs. Cadinol, or a mixture of cadinols, occurs also in West Indian sandalwood oil.‡ The presence of cadinol in French lavender oil has been shown by Seidel, Müller and Schinz§ by isolation of cadinene dihydrochloride from the tertiary sesquiterpene alcohol fraction. Plattner and Markus|| have recently described the isolation of an interesting crystalline cadinol from Javanese citronella oil. The properties of this substance are discussed further on p. 139.¶

Cadinol does not react with phthalic anhydride at 110° and it must therefore be a tertiary alcohol and, since it contains one

* *Ber.* 1914, **47**, 2073.

† *J.C.S.* 1926, p. 2811.

‡ Ruzicka, Capato and Huyser, *Rec. trav. chim.* 1928, **47**, 370; Deussen and Awramoff, *J. pr. Chem.* 1928 [ii], **120**, 123.

§ *Helv. Chim. Acta*, 1944, **27**, 738.

|| *Ibid.* 1942, **25**, 1674.

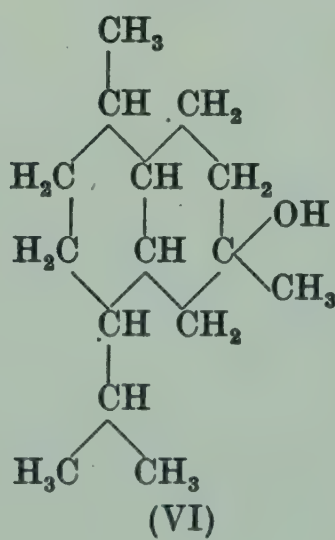
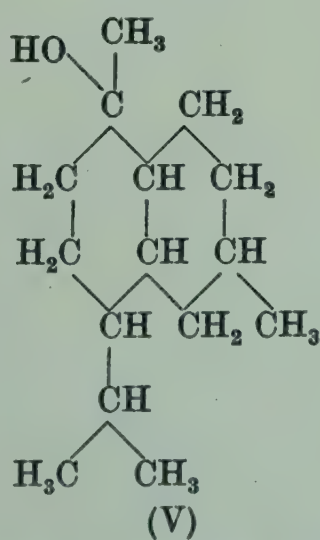
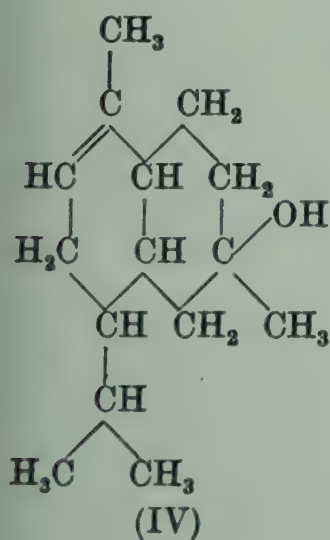
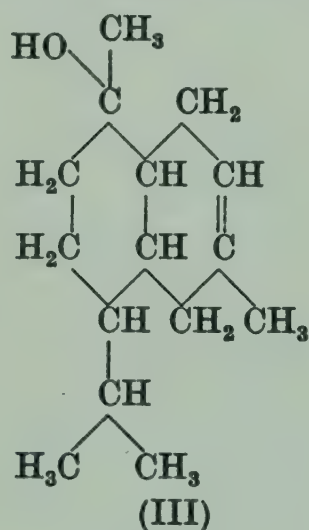
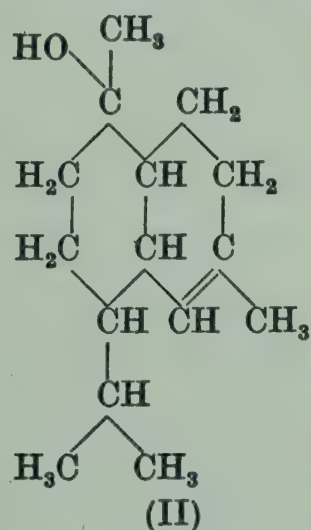
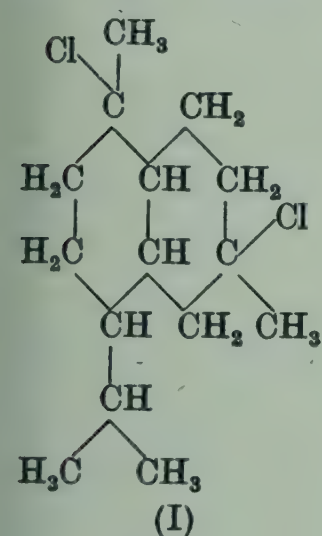
¶ The sesquiterpene alcohol, *kiganol*, isolated by Kimura and Mizoshita (*Mem. Coll. Sci. Kyoto*, 1931, A **14**, 273) from the wood oil of *Cryptomeria japonica* is probably identical with cadinol. A similar identity is probable also between the sesquiterpene alcohol, *fokienol* (Glichitch, *Compt. rend.* 1930, **191**, 1457), from the essential oil of *Fokienia Hodginsii* and cadinol.

ethylenic linkage and yields cadinene dihydrochloride (I), it may be represented by either of the formulae (II), (III) or (IV), α -, β - and γ -cadinols.

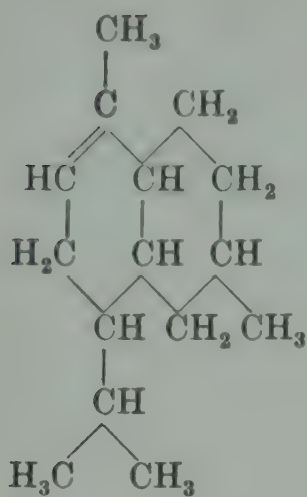
The investigations of Ruzicka and Stoll* have shown that *d*-cadinol is probably a mixture of all three isomerides, consisting, however, mainly of the α - and β -forms.

On catalytic hydrogenation of *d*-cadinol, *d*-dihydrocadinol, $C_{15}H_{28}O$, b.p. $150-153^{\circ}/12$ mm., $d_4^{16^{\circ}} 0.9579$, $n_D^{16^{\circ}} 1.4948$, $\alpha_D + 23^{\circ}$, is obtained, which must have either formula (V) or (VI). When the saturated alcohol is dehydrated with formic acid, it yields *dihydrocadinene*, $C_{15}H_{26}$, b.p. $129-131^{\circ}/10$ mm., $d_4^{13^{\circ}} 0.8999$, $n_D^{13^{\circ}} 1.4952$, for which the most probable formulae are (VII), (VIII) or (IX).

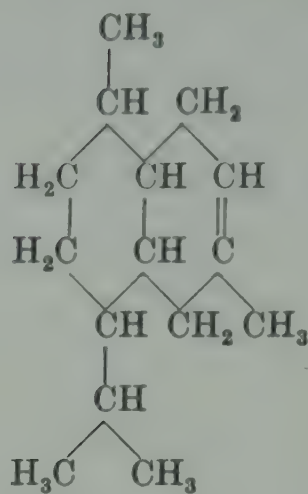
On ozonolysis, dihydrocadinene gave a neutral substance, $C_{15}H_{26}O_2$, b.p. $110^{\circ}/0.2$ mm., and an acid, $C_{15}H_{26}O_3$, b.p. $140^{\circ}/0.2$ mm., which were probably the *ketonic-aldehyde* (X) and the corresponding ketonic acid. The formation of these substances indicated that dihydrocadinene consisted essentially of



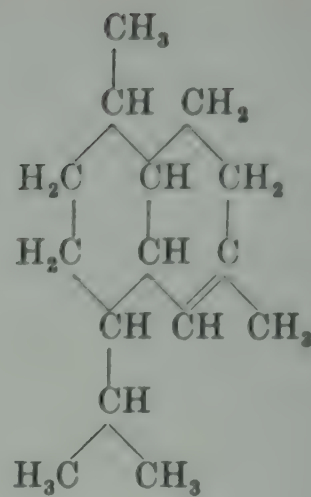
* *Helv. Chim. Acta*, 1924, 7, 94.



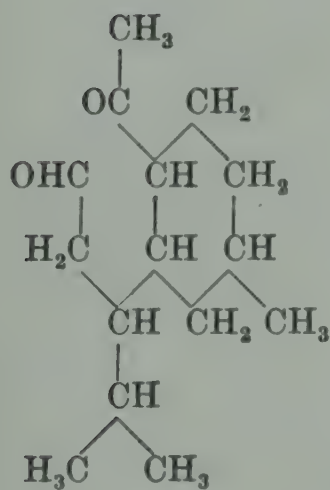
(VII)



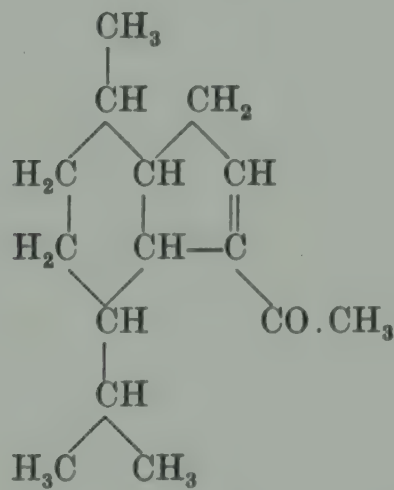
(VIII)



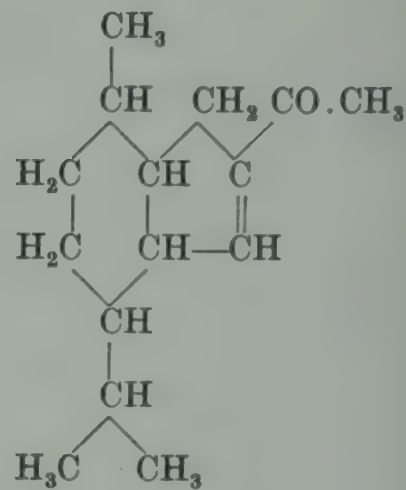
(IX)



(X)



(XI)



(XII)

a hydrocarbon having the structure (VII), since, if either of the hydrocarbons (VIII) or (IX) had been present in considerable amount, formation of the dicyclic ketones (XI) and (XII) might have been anticipated. "Cadinol" consists therefore mainly of the two alcohols, α - and β -cadinols, and this was confirmed by a study of the products which were formed on the ozonolysis of the alcohol itself. If it is assumed that the reaction proceeds normally, then a mixture of the two alcohols (II) and (III) should yield the *hydroxy-ketonic-aldehydes* (XIII) and (XIV), which would pass by internal condensation into the unsaturated *hydroxy-ketones* (XV) and (XVI). These would, on dehydration, yield the unsaturated *ketones* (XVII) and (XVIII) (p. 140).

On oxidation with ozone *d*-cadinol gave a neutral substance, $\text{C}_{15}\text{H}_{24}\text{O}_2$, b.p. 180–184°/12 mm., which was probably a mixture of (XV) and (XVI) and this, on digestion with formic acid, was

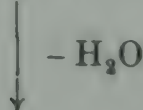
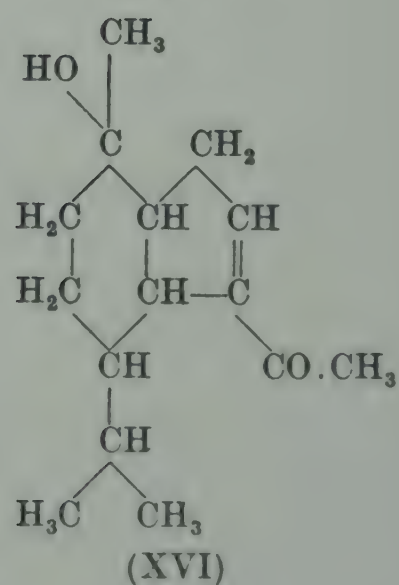
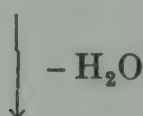
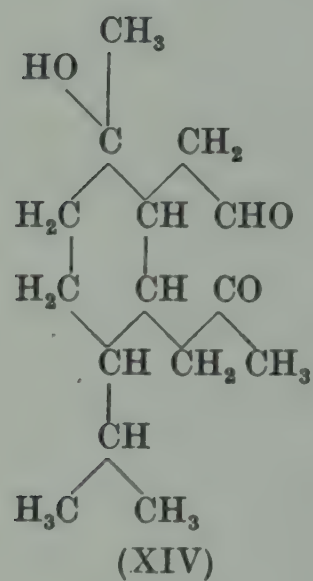
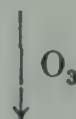
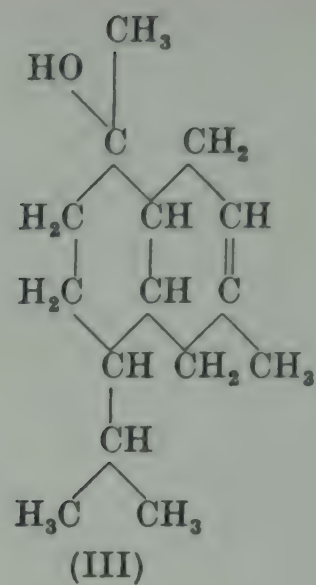
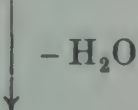
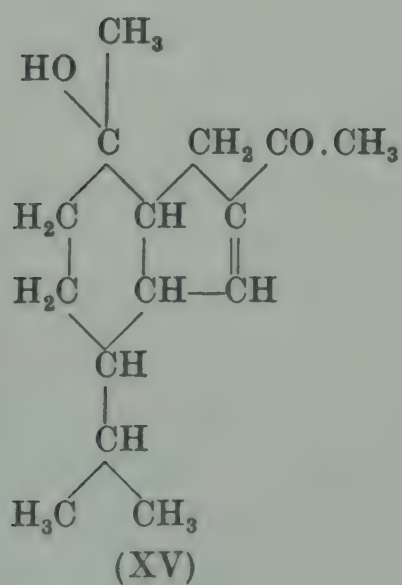
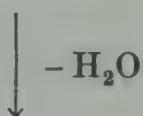
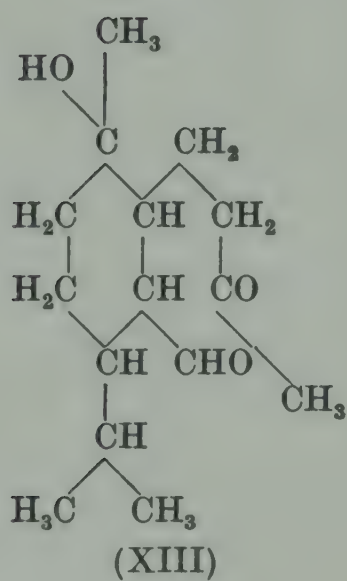
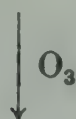
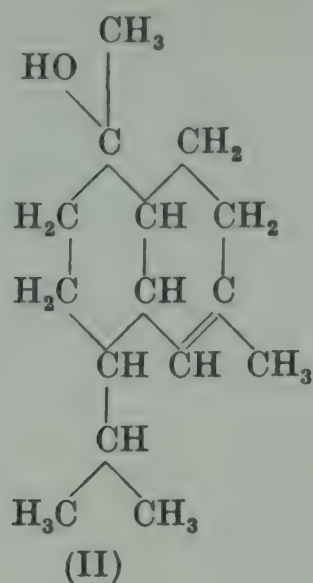
dehydrated to a substance, $C_{15}H_{22}O$, b.p. $140-145^{\circ}/12$ mm. This substance could not be characterised by the preparation of any crystalline derivatives, but since, on oxidation with manganese dioxide and sulphuric acid, it gave a mixture of mellophanic and trimellitic acids (XIX) and (XX) (p. 141), it may be assumed that it was a mixture of the unsaturated ketones (XVII) and (XVIII).

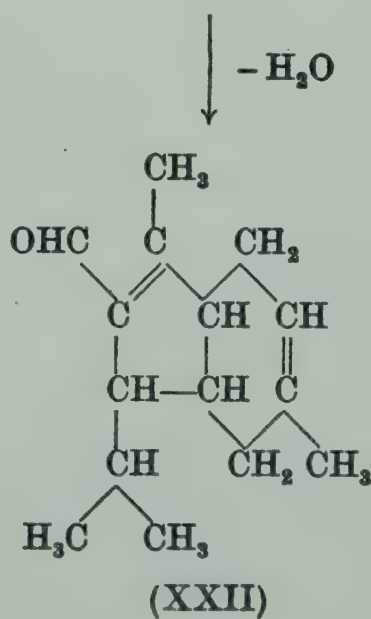
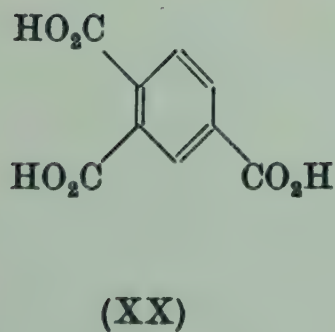
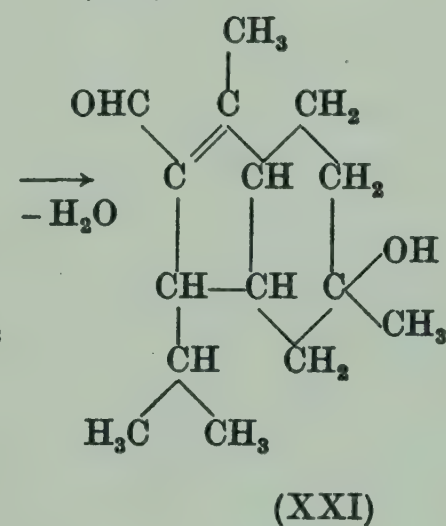
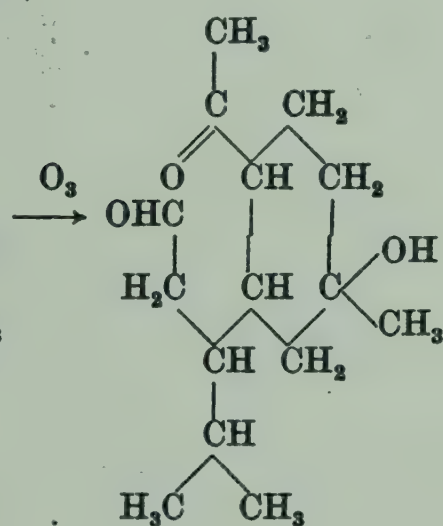
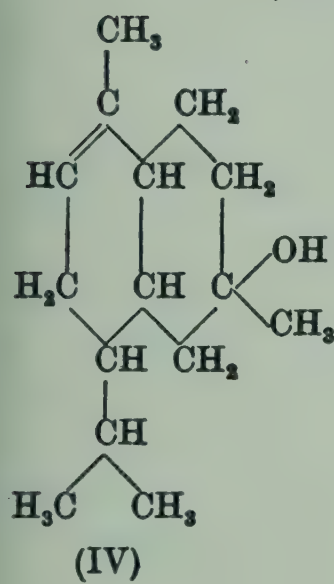
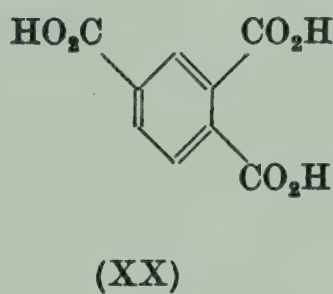
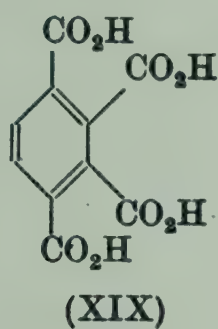
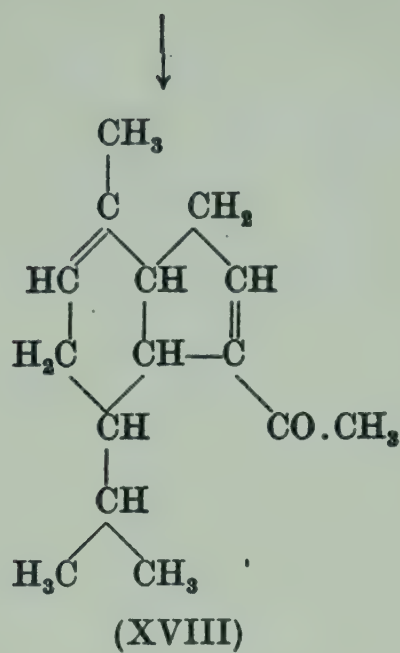
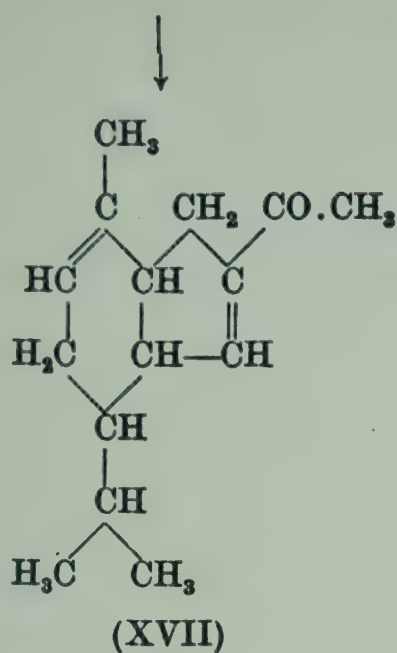
Whilst mellophanic acid (XIX) would result from the oxidation of either (XVII) or (XVIII), they could neither of them yield trimellitic acid (XX). The formation of this acid is probably due to the presence in *d*-cadinol of γ -cadinol (IV), which would on ozonolysis give an *hydroxy-aldehyde* (XXI) and this would, on dehydration, give the unsaturated *aldehyde* (XXII). This aldehyde should on oxidation yield trimellitic acid (XX).

These experiments, which involve very great experimental difficulties, seem to admit of no other conclusion than that *d*-cadinol is a mixture of the three alcohols, α -, β - and γ -cadinols, in which the two former probably predominate.

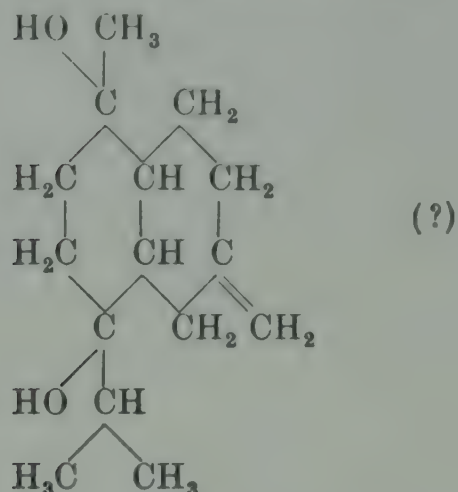
d-Cadinol is a colourless oil, b.p. $155-156^{\circ}/12$ mm., $d_4^{14^{\circ}}$ 0.9665, $n_D^{14^{\circ}}$ 1.5054, $\alpha_D + 7.7^{\circ}$, whilst for *l*-cadinol Henderson and Robertson found b.p. $153-155^{\circ}/10$ mm., $d^{20^{\circ}}$ 0.9727, $n_D^{20^{\circ}}$ 1.508, $[\alpha]_{5461} - 54^{\circ}$. It can be identified by conversion into cadinene dihydrochloride. When it is heated with zinc dust under pressure at 300° it is dehydrated to cadinene.

The relationship of the crystalline cadinol, m.p. 72.5° , $[\alpha]_D - 39.4^{\circ}$ (in chloroform), *p*-nitrobenzoate, m.p. 136° , $[\alpha]_D - 6.76^{\circ}$ (in chloroform), of Plattner and Markus (see p. 136) to the liquid alcohols discussed above has not been determined. Since it is stated to give cadinene on dehydration it must be represented by one of the formulae (II), (III) or (IV). Hydrogenation in alcoholic solution using a Raney nickel catalyst gave a *dihydro-cadinol*, m.p. 124.5° , $[\alpha]_D - 72.5^{\circ}$ (in chloroform). From this alcohol a dihydrocadinene was prepared by dehydration, but no identifiable products could be isolated on oxidation with either ozone or chromic acid, so that its structure is unknown.





CALAMENDIOL



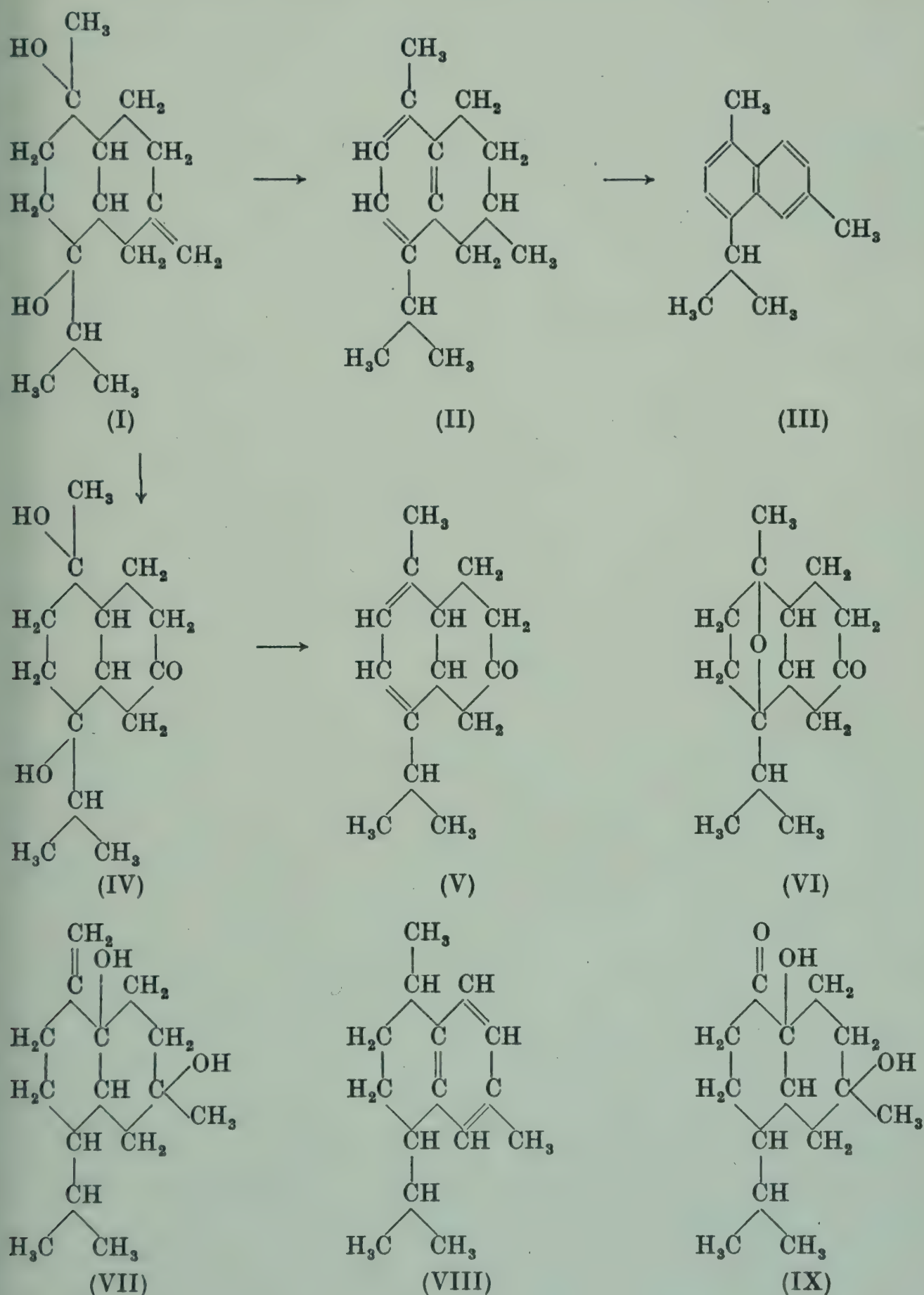
In addition to calamenol (see p. 190), the oil from *Acorus Calamus* contains a substance, $\text{C}_{15}\text{H}_{26}\text{O}_2$, m.p. 169° , subliming at $65\text{--}75^\circ/0.006$ mm., $[\alpha]_D^{17^\circ} - 4.4^\circ$, formerly called calameone. Böhme* showed that this compound was a bicyclic sesquiterpene ditertiary alcohol containing one ethylenic linkage, and it is therefore more correctly called *calamendiol*.

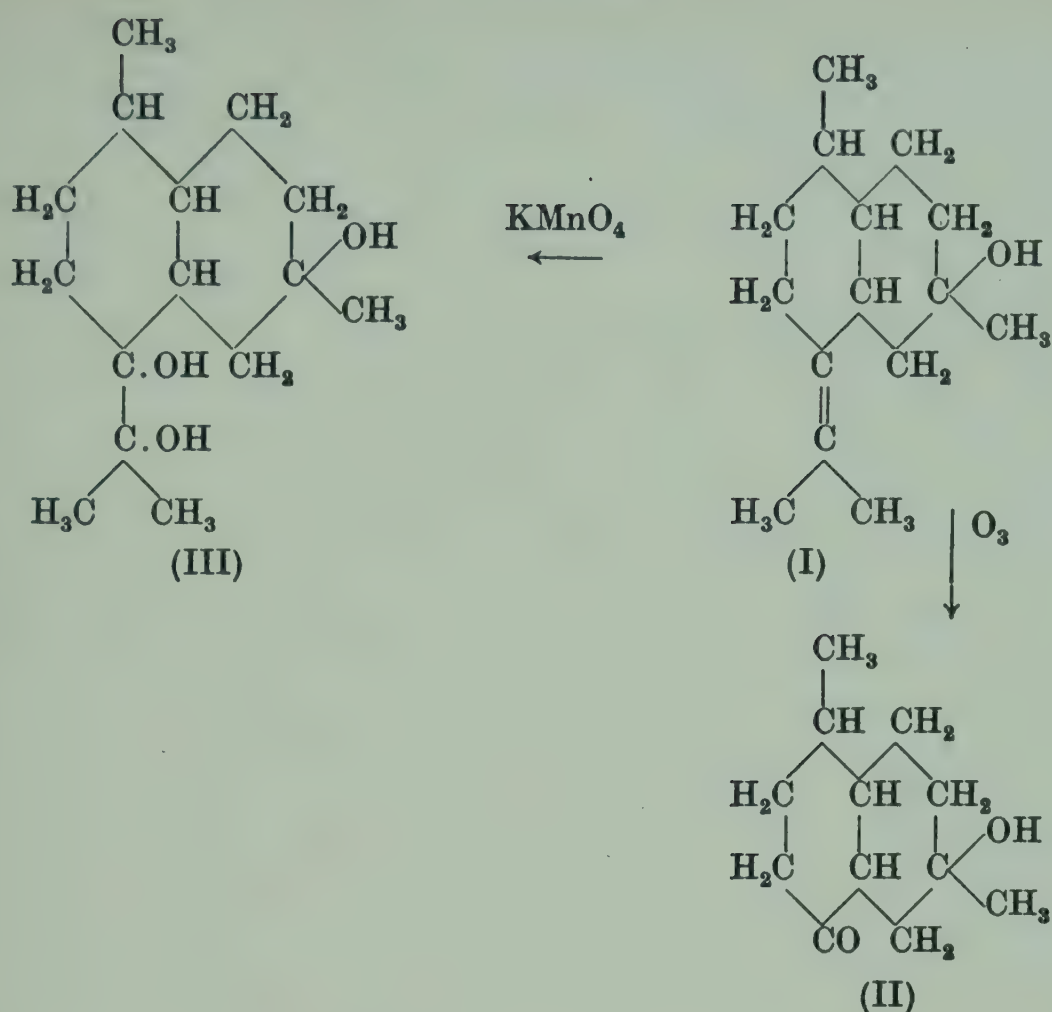
The probable constitution (I) assigned to calamendiol is based, principally, upon the investigation of its chemistry carried out by Treibs.† On dehydration with 50 per cent sulphuric or hot formic acid calamendiol afforded a partially aromatic *hydrocarbon* (II), $\text{C}_{15}\text{H}_{22}$, b.p. $137\text{--}139^\circ/12$ mm., $d_4^{20^\circ} 0.9314$, $n_D^{20^\circ} 1.5214$, $\alpha_D^{17^\circ} - 6.60^\circ$, smoothly dehydrogenated by selenium to give cadalene (III). Ozonolysis of calamendiol furnished a crystalline *dihydroxyketone*, $\text{C}_{14}\text{H}_{24}\text{O}_3$ (IV), m.p. $167.5\text{--}168^\circ$, and formaldehyde. Attempted hypobromite oxidation indicated that (IV) was not a methyl ketone, whilst treatment with hot formic acid, or more simply distillation at atmospheric pressure, gave an unsaturated *ketone*, $\text{C}_{14}\text{H}_{20}\text{O}$ (V), b.p. $150\text{--}156^\circ/10$ mm., $d_4^{20^\circ} 1.0201$, $n_D^{20^\circ} 1.5444$, $\alpha_D^{20^\circ} - 19.35^\circ$, which showed little tendency to isomerise to a phenol. Whilst acetylation of calamendiol by heating with acetic anhydride gave a *monoacetate*, $\text{C}_{17}\text{H}_{28}\text{O}_3$, m.p. $84\text{--}85^\circ$, b.p. $152\text{--}162^\circ/6$ mm., the dihydroxy-ketone (IV), under the same conditions, afforded a cyclic *ether*, $\text{C}_{14}\text{H}_{22}\text{O}_2$ (VI), b.p. $172\text{--}185^\circ/6$ mm., $d_4^{20^\circ} 1.0610$, $n_D^{20^\circ} 1.5165$, $\alpha_D^{20^\circ} - 10^\circ$.

* *Arch. Pharm.* 1940, **278**, 1; compare Thoms and Beckström, *Ber.* 1901, **34**, 1021; 1902, **35**, 3187, 3195; Šorm and Herout, *Coll. Czech. Chem. Comm.* 1948, **13**, 177.

† *Chem. Ber.* 1949, **82**, 530.

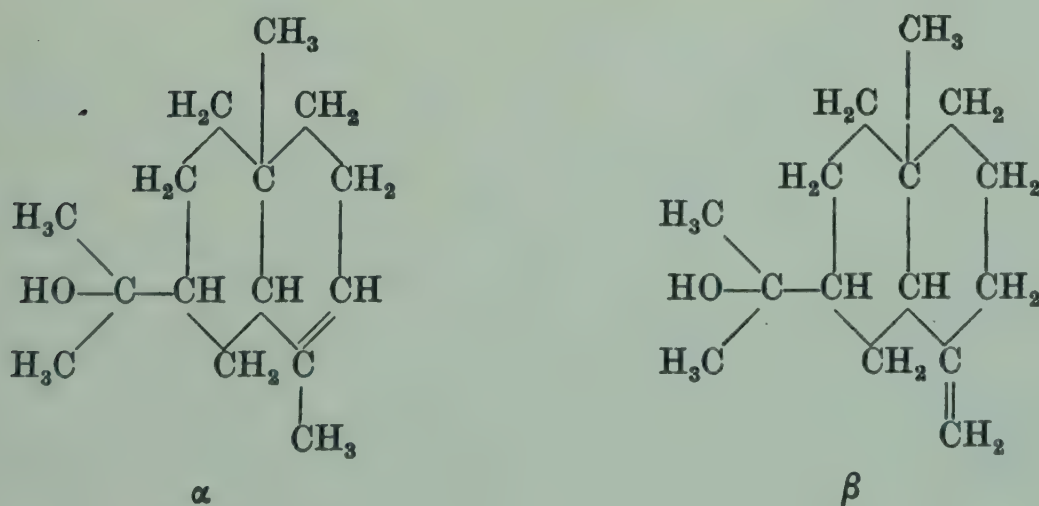
Although these experiments are in agreement with the formula (I) given above they do not seem to exclude the constitution (VII). If the latter were correct then the partially aromatic hydrocarbon would be (VIII) and the dihydroxyketone obtained by ozonolysis of calamendiol would be (IX). The latter





Torreyol, m.p. $139-140^\circ$, $[\alpha]_D + 107.1^\circ$, gave on catalytic hydrogenation *dihydrotorreyol*, m.p. $106-107^\circ$, $[\alpha]_D - 10.8^\circ$. On digestion of torreyol with formic acid elimination of water occurs with the formation of the hydrocarbon, *torreyene*, b.p. $89-90^\circ/1 \text{ mm.}$, $[\alpha]_D + 46.7^\circ$ (*dihydrochloride*, m.p. $118-119^\circ$), which gave on ozonolysis acetone. No evidence is available as to the position of the second ethylenic linkage in the hydrocarbon.

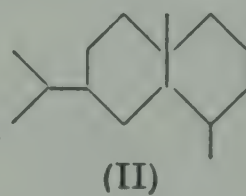
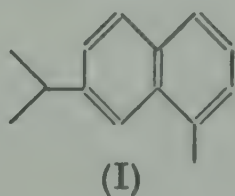
EUDESMOL (SELINENOL)



The crystalline sesquiterpene alcohol, *eudesmol*, $C_{15}H_{26}O$,* was first isolated by Baker and Smith† from the oil derived from *Eucalyptus piperita* and it has since been found to occur in various other eucalyptus oils,‡ the most convenient source being *E. Macarthuri*.

Eudesmol, m.p. $82-83^{\circ}$, b.p. $156^{\circ}/10\text{ mm.}$, $d^{20^{\circ}} 0.9884$, $n_D^{20^{\circ}} 1.516$, $[\alpha]_D + 31.3^{\circ}$ (in chloroform), was considered by Smith to have the composition $C_{10}H_{16}O$ and to be an oxide. This was later found to be incorrect, eudesmol being an alcohol and having the composition $C_{15}H_{26}O$. From its physical constants it appeared probable that it was a dicyclic alcohol containing one ethylenic linkage and this was confirmed by the investigations of Semmler and Tobias.§ They found that eudesmol could be acetylated, giving *eudesmol acetate*, b.p. $165-170^{\circ}/11\text{ mm.}$, $d^{20^{\circ}} 0.9933$, $n_D^{20^{\circ}} 1.4920$, $[\alpha]_D + 31^{\circ}$, whilst on catalytic hydrogenation *dihydroeudesmol* (*dihydroselinenol*), $C_{15}H_{28}O$, m.p. $84-85^{\circ}$, was obtained. Semmler and his collaborators attempted to determine the constitution of the alcohol and also of the hydrocarbon, *eudesmene*, prepared from it by dehydration, but they were unable to obtain any characteristic degradation products by oxidation either with ozone or potassium permanganate.

For our knowledge of the structure of eudesmol we are indebted to the prolonged experiments of Ruzicka and his co-workers.|| By dehydrogenation with sulphur or selenium eudalene (I) was obtained, which determined the relative positions of fourteen of



* The alcohol, *uncineol*, described by Baker and Smith (*J. Proc. Roy. Soc. New South Wales*, 1907, **41**, 196) as occurring in the oil from *Melaleuca uncinata*, has been shown by Penfold (*ibid.* 1925, **49**, 124) to be identical with eudesmol, whilst Ruzicka, Koolhaas and Wind (*Helv. Chim. Acta*, 1931, **14**, 1178) have found *machilol* from the oil of *Machilus Kusanoi* (*Schimmel's Report*, 1914, **1**, 101; Takagi, *J. Pharm. Soc. Japan*, 1921, **473**, 1) and *atractylol* from *Atractylis ovata* (Gadamer and Amenomiya, *Arch. Pharm.* 1903, **241**, 23; Takagi, *J. Pharm. Soc. Japan*, 1921, **473**, 1) to be identical also with this alcohol.

† *J. Proc. Roy. Soc. New South Wales*, 1897, **31**, 195.

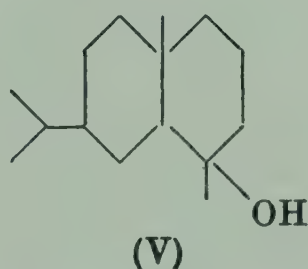
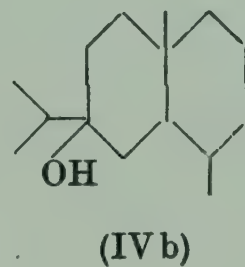
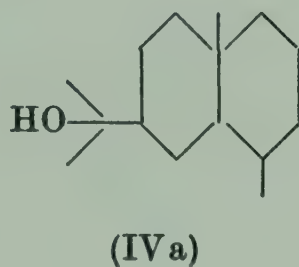
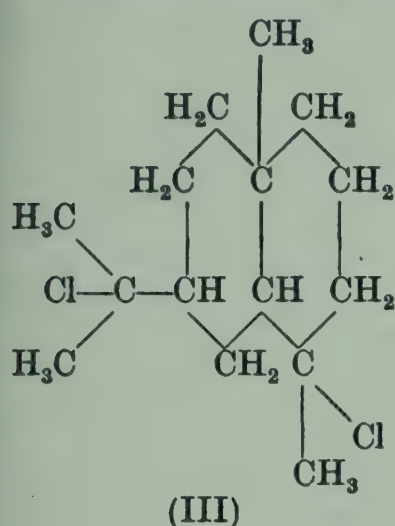
‡ Baker and Smith, *A Research on the Eucalypts*, 2nd ed. 1920.

§ *Ber.* 1913, **46**, 2026; compare Semmler and Risse, *ibid.* 2303.

|| Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, **5**, 362; Ruzicka and Capato, *Annalen*, 1927, **453**, 62; Ruzicka, Wind and Koolhaas, *Helv. Chim. Acta*, 1931, **14**, 1132.

the fifteen carbon atoms present in the alcohol. From analogy with selinene and for the reasons given on p. 5 it was probable, therefore, that the alcohol had the carbon skeleton (II) and it remained only to determine the position of the ethylenic linkage and the hydroxyl group.

On treatment with hydrogen chloride, either in acetic acid or ethereal solution eudesmol yields a *dihydrochloride*, m.p. 74–75°, $[\alpha]_D + 20^\circ$, which is undoubtedly identical with the selinene dihydrochloride (III) described by Schimmel and Co.,* although Ruzicka, Wind and Koolhaas have been unable to prepare from the hydrocarbon a dihydrochloride having this melting-point.

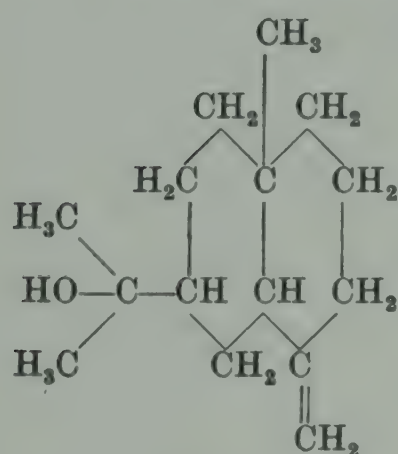


It follows therefore that the hydroxyl group must be in one or the other of the positions shown in the skeleton formulae (IV a), (IV b) and (V).

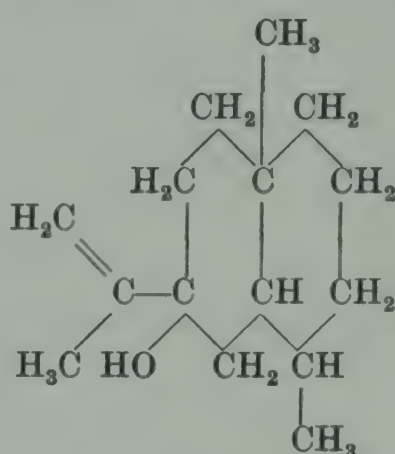
Proof of the position of the hydroxyl group, and also of the ethylenic linkage, was furnished by the oxidation of eudesmol with ozone, when a *ketonic alcohol*, $C_{14}H_{24}O_2$, m.p. 119–120°, was obtained which gave on dehydration with formic acid an unsaturated *ketone*, $C_{14}H_{22}O$. This ketone, which boiled over a somewhat wide range, 130–150°/12 mm., was probably a mixture of isomerides, since it gave two *semicarbazones*, m.p. 215° and 235° respectively. The formation of a ketonic alcohol with the loss of only one carbon atom showed that in eudesmol the

* Schimmel's Report, 1910, p. 97.

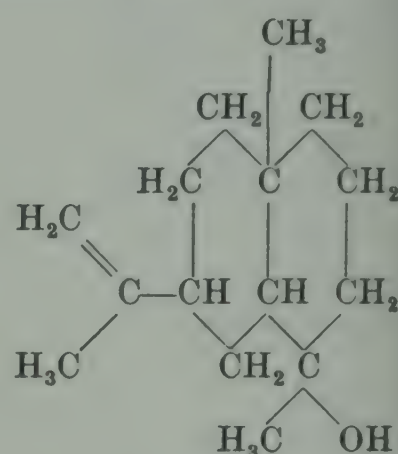
ethylenic linkage must be exocyclic, with either of the structures (VI), (VII) or (VIII), when the ketonic alcohol would be represented by (IX), (X) or (XI). For the unsaturated ketone eight formulae are possible, but it must be either (XII) or (XIII) (in all probability a mixture of the two), since on reduction with sodium in ethyl alcoholic solution it yields an unsaturated *alcohol*, $C_{14}H_{24}O$, b.p. $145-146^{\circ}/12$ mm. This alcohol, probably a mixture of (XIV) and (XV), gives on dehydrogenation with sulphur



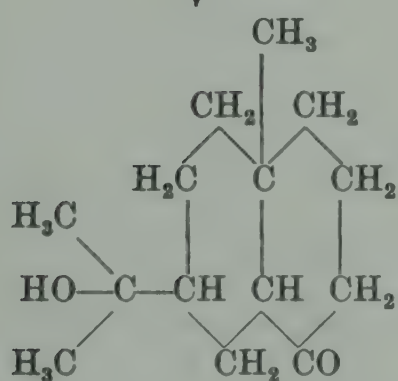
(VI)



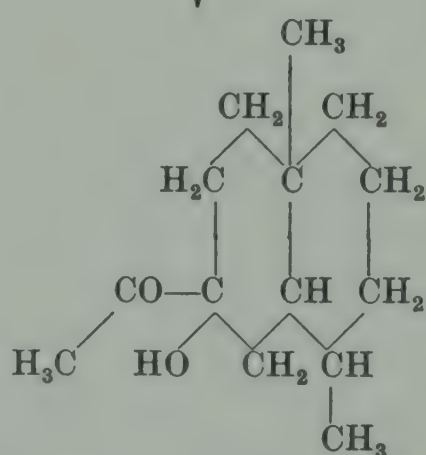
(VII)



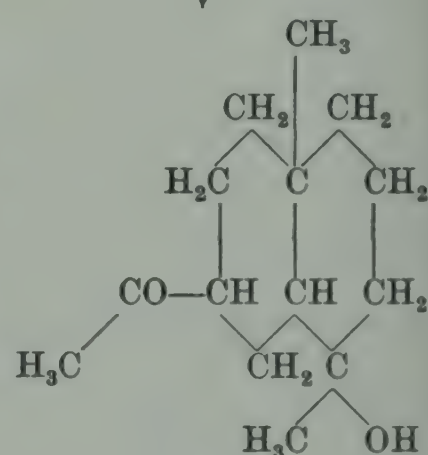
(VIII)



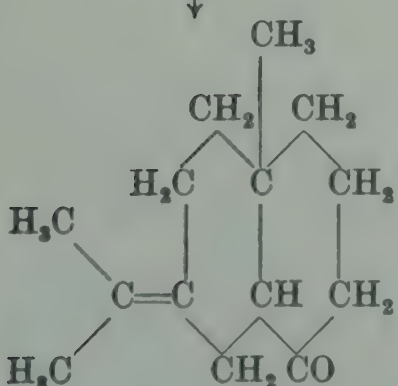
(IX)



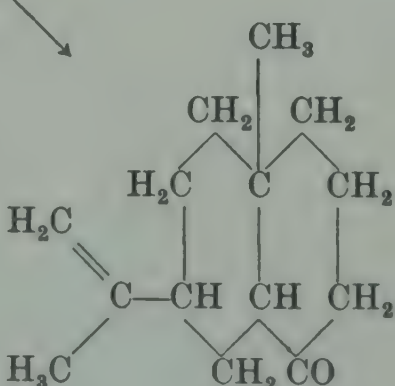
(X)



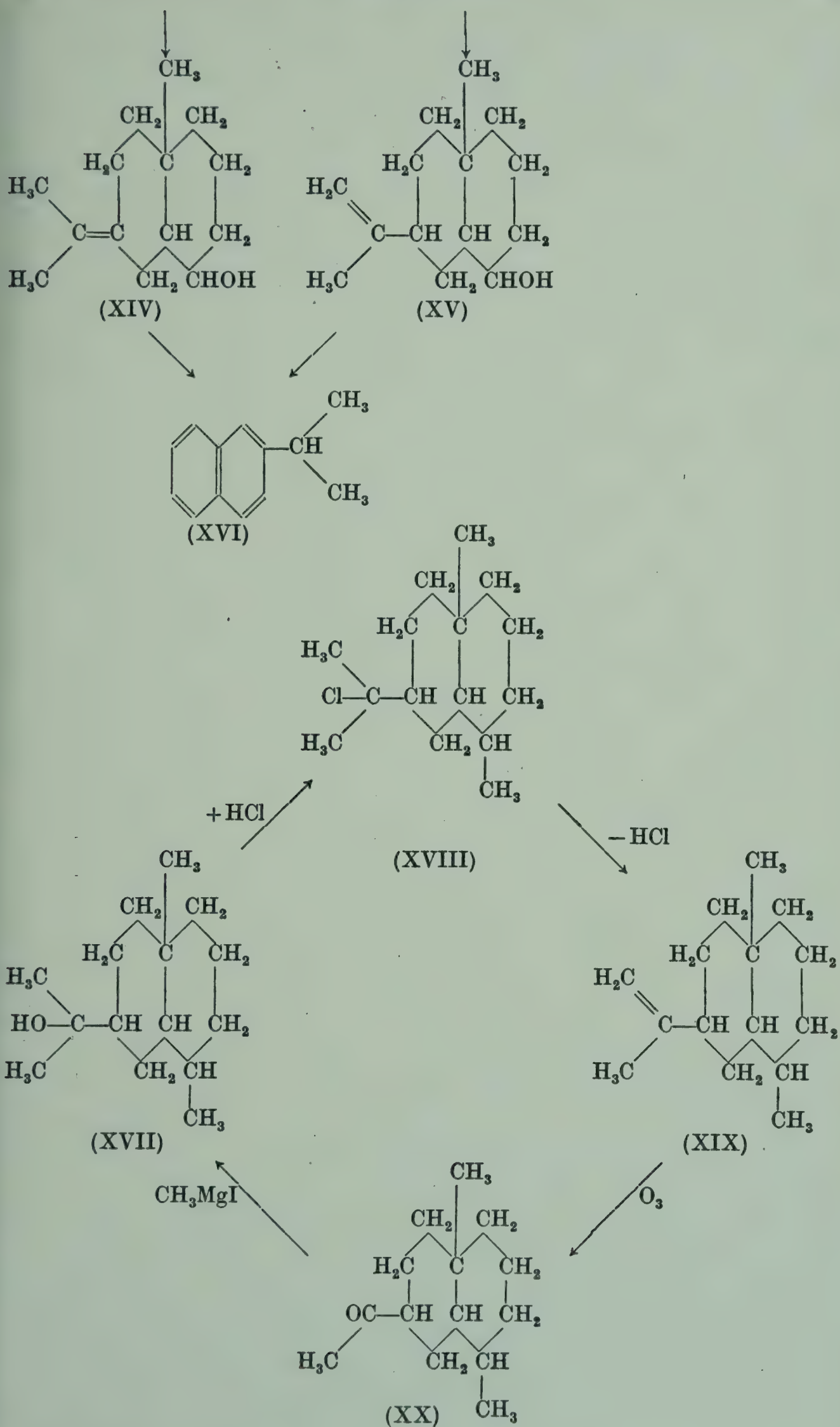
(XI)



(XII)



(XIII)

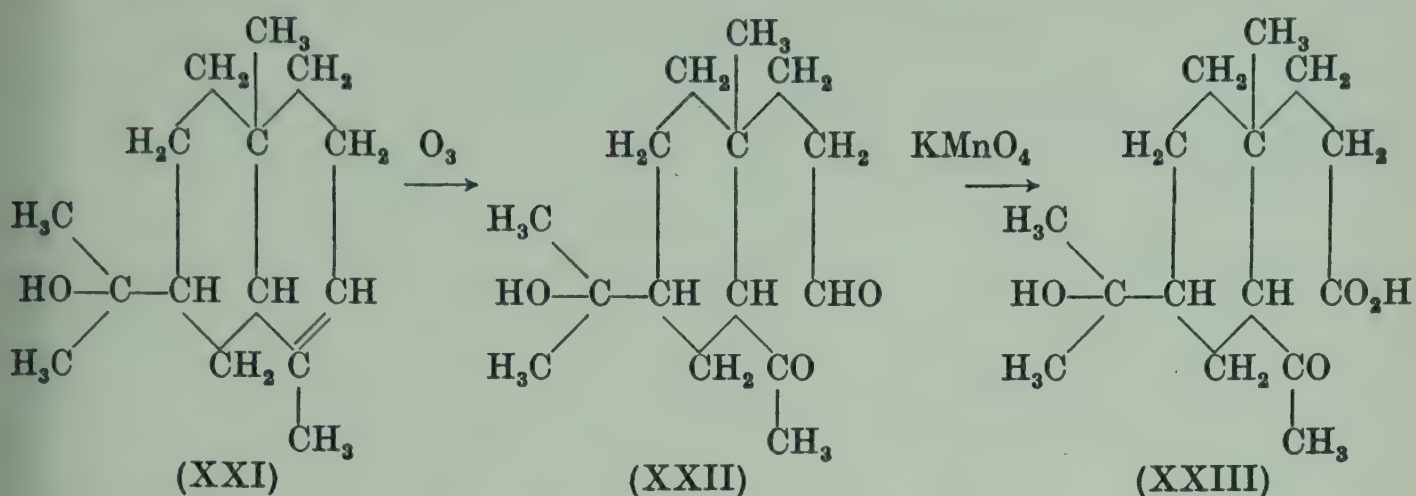


β -isopropyl n aphthalene (XVI), b.p. 125°/12 mm., *picrate*, m.p. 91°, which was identified by comparison with a synthetic specimen.

These experiments leave little doubt that eudesmol is correctly represented by (VI), but additional proof was obtained by two other methods. As mentioned on p. 36, it had been observed by Semmler and Risse* that when selinene dihydrochloride was treated with milk of lime a liquid sesquiterpene alcohol, *selinenol*, $C_{15}H_{26}O$, was formed, which on catalytic hydrogenation gave a saturated alcohol, *dihydroselenol*, $C_{15}H_{28}O$, m.p. 86–87°. Ruzicka, Wind and Koolhaas on repeating these experiments, but using the selinene dihydrochloride, m.p. 52°, obtained a crystalline sesquiterpene alcohol, m.p. 78–79°, $[\alpha]_D + 38^\circ$, which did not depress the melting-point of pure eudesmol, m.p. 82–83°, $[\alpha]_D + 31^\circ$. The identity of the two alcohols was confirmed by a comparison of *dihydroeudesmol*, m.p. 84–85°, $[\alpha]_D + 17^\circ$, prepared by the catalytic hydrogenation of eudesmol and *dihydroselenol*, m.p. 85–86°, $[\alpha]_D + 17^\circ$, obtained from selinenol. The same investigators found also that when dihydroeudesmol (XVII) was converted into the corresponding *hydrochloride* (XVIII) and this treated with either aniline or alcoholic potassium hydroxide, *dihydroeudesmene* (*dihydroselinene*) (XIX), b.p. 132–133°/10 mm., $d_4^{20^\circ} 0.9080$, $n_D^{20^\circ} 1.4972$, was obtained. Oxidation of this hydrocarbon with ozone gave 5:9-dimethyl-3-acetyldecalin (XX), b.p. 145–147°/12 mm., $d_4^{22^\circ} 0.9634$, $n_D^{22^\circ} 1.4904$, *semicarbazone*, m.p. 206°. By the action of methyl magnesium iodide on this ketone dihydroeudesmol was obtained, and in this manner a partial synthesis of the alcohol has been achieved.

As has been so frequently observed in terpene chemistry, even with crystalline substances, eudesmol, although apparently homogeneous, has been found to be a mixture. When eudesmol was oxidised with ozone, in addition to the ketonic alcohol referred to above, a *hydroxy ketonic aldehyde*, $C_{15}H_{26}O_3$, the *semicarbazone* of which melted at about 145°, was isolated; this aldehyde on oxidation with potassium permanganate gave an *acid*, $C_{15}H_{26}O_4$, the *ethyl* ester of which boiled at 160–175°/0.15 mm. The formation of these degradation products can only be explained if eudesmol is a mixture of β -eudesmol (VI) (p. 148) and

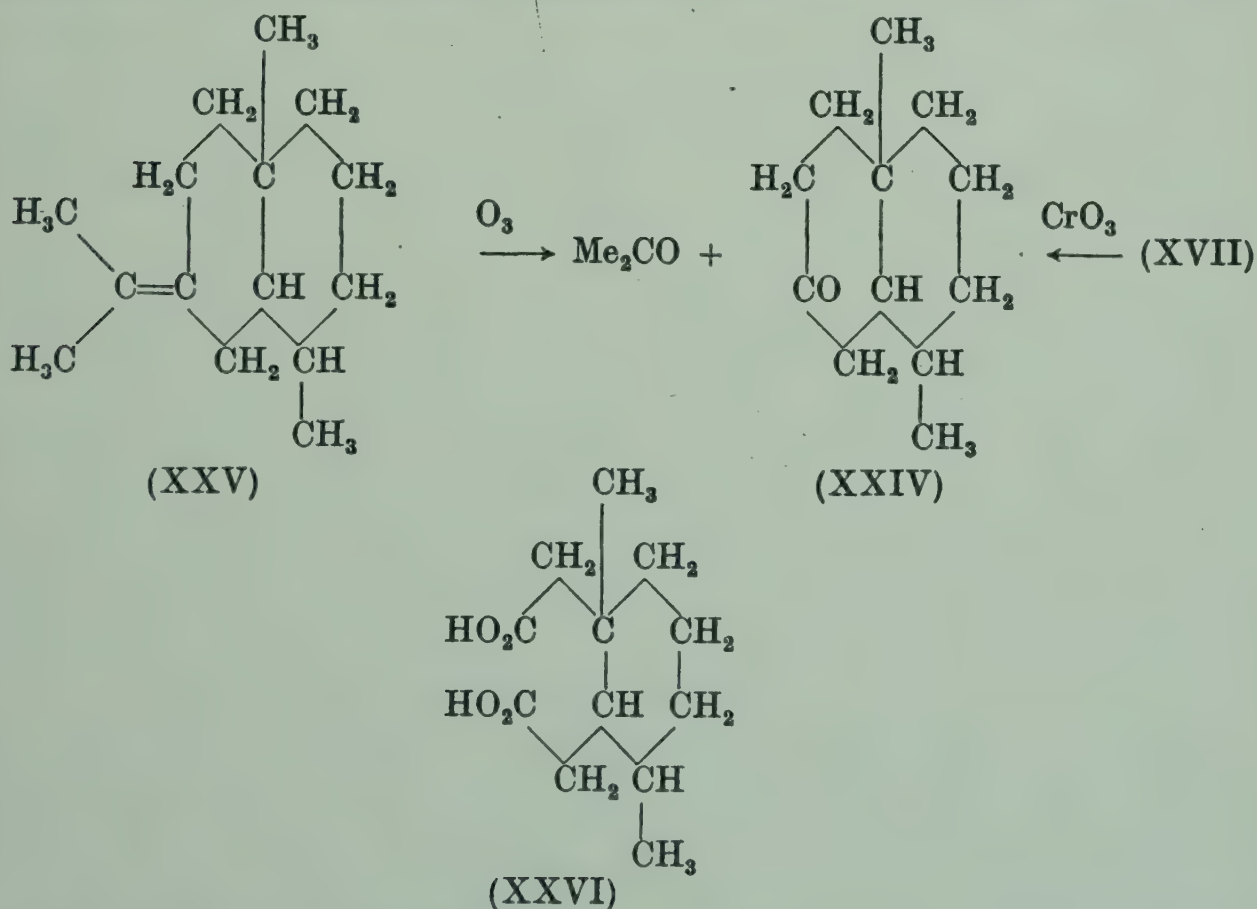
* Ber. 1912, 45, 3305.



α -eudesmol (XXI), when the hydroxy ketonic aldehyde would be (XXII) and the acid (XXIII).

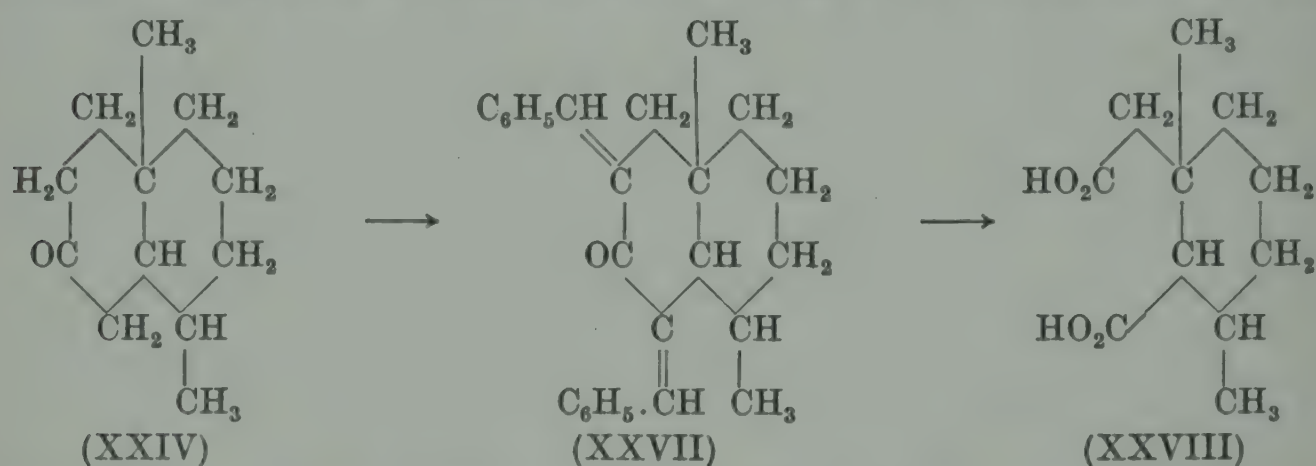
The relative proportions of α - and β -eudesmol present in the natural "eudesmol" would appear to show considerable variations without appreciably affecting either the melting-point or the optical rotatory power. According to Ruzicka, Wind and Koolhaas eudesmol prepared from selinene is mainly the α -alcohol, whilst "machilol" consists essentially of the β -alcohol.

It was mentioned above that ozonolysis of dihydroeudesmene (XIX) gave 5:9-dimethyl-3-acetyldecalin (XX); Ruzicka, Plattner and Fürst* have re-examined this oxidation and find that acetone and 5:9-dimethyl-3-decalone (XXIV), b.p. 75–90°/1 mm.,



* *Helv. Chim. Acta*, 1942, 25, 1364; compare Ruzicka and Capato, *Annalen*, 1927, 453, 82.

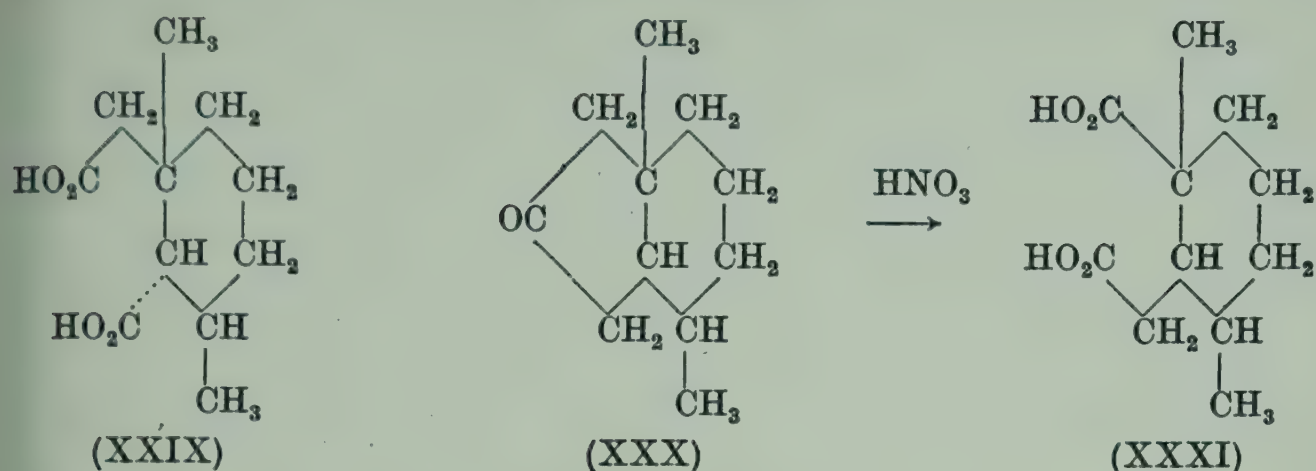
n_D^{20} 1.488 to 1.497, *semicarbazone*, m.p. 222° , $[\alpha]_D + 26^\circ$ (in acetic acid), are also formed, though the yields are poor and depend on the method of preparation of the dihydroeudesmene. This latter hydrocarbon must therefore be a mixture of (XIX) (p. 149) and its *isopropylidene* isomer (XXV). The ketone (XXIV) is, however, prepared far more conveniently by chromic acid oxidation of dihydroeudesmol (XVII), the *dicarboxylic acid*, $C_{12}H_{20}O_4$ (XXVI), m.p. $141-143^\circ$, *dimethyl ester*, d_4^{20} 1.055, n_D^{20} 1.4684, $[\alpha]_D + 5^\circ$ (in acetone) being formed at the same time. 5:9-Dimethyl-3-decalone forms a *monobenzal* derivative, m.p. $141-143^\circ$, $[\alpha]_D + 20.63^\circ$ (in alcohol), and a *dibenzal derivative* (XXVII), m.p. $198-200^\circ$, $[\alpha]_D - 14.6^\circ$ (in chloroform), which on ozonolysis gives the *dicarboxylic acid*, $C_{11}H_{18}O_4$ (XXVIII), m.p. $132-134^\circ$, $[\alpha]_D + 47.1^\circ$ (in acetone), *dimethyl ester*, b.p. $80-81^\circ/1\text{ mm.}$, d^{20} 1.0562, n_D^{20} 1.4645, $[\alpha]_D + 45.3^\circ$ (in acetone), *anilide methyl ester*, m.p. $100-102^\circ$, $[\alpha]_D + 78^\circ$ (in acetone). The



properties of the dicarboxylic acid (XXVIII) have been further investigated by Plattner, Fürst and Hellerbach.* With acetic anhydride it gives an *anhydride*, $C_{11}H_{16}O_3$, m.p. $101-102^\circ$, whilst on heating with concentrated hydrochloric acid at 195° it yields an isomeric *dicarboxylic acid*, $C_{11}H_{18}O_4$, m.p. $156.5-157.5^\circ$, $[\alpha]_D - 7.3^\circ$ (in acetone), *anhydride*, m.p. 46° . The formation of this isomeric dicarboxylic acid is a confirmation of the view that the ring fusion in eudesmol and related compounds is *cis* (see p. 6). It should be formulated, therefore, as (XXIX).

When 5:9-dimethyl-3-decalone (XXIV) was oxidised with sodium hypobromite it gave the expected dicarboxylic acid (XXVI), which was cyclised to a *ketone*, $C_{11}H_{18}O$ (XXX), *semicarbazone*, m.p. $238-239^\circ$. Oxidation of this ketone with

* *Helv. Chim. Acta*, 1947, **30**, 2158.



nitric acid furnished a dicarboxylic acid, $\text{C}_{11}\text{H}_{18}\text{O}_4$ (XXXI), m.p. $195\text{--}196^\circ$, $[\alpha]_D + 49.9^\circ$ (in acetone), *anhydride*, m.p. $92\text{--}94^\circ$, isomeric with (XXVIII), which, as would be anticipated, was not isomerised on heating with hydrochloric acid. The acid (XXXI) gave a *dimethyl ester*, $d_4^{20.5^\circ} 1.0641$, $n_D^{20.5^\circ} 1.4645$, and a *monoethyl ester*, $\text{C}_{13}\text{H}_{22}\text{O}_4$, b.p. $155^\circ/0.05\text{ mm.}$, *amide*, m.p. 132° . These experiments confirm the already assigned position of the angular methyl group in eudesmol and related compounds.

Eudesmol, which can be readily identified by its melting-point, may be characterised by the preparation of the dihydrochloride or dihydrobromide, whilst according to Smith it gives, when brominated in acetic acid solution, a *dibromide*, m.p. $55\text{--}56^\circ$.

Although eudesmol, as mentioned above, gives dihydro-eudesmol on catalytic hydrogenation in ethereal solution, if the reduction is carried out in acetic acid solution replacement of the hydroxyl group by hydrogen occurs also, with the formation of *tetrahydroeudesmene* (*tetrahydroselinene*),* $\text{C}_{15}\text{H}_{28}$, b.p. $117^\circ/5.5\text{ mm.}$, $d^{20^\circ} 0.8896$, $n_D 1.4842$, $[\alpha]_D + 11.48^\circ$.

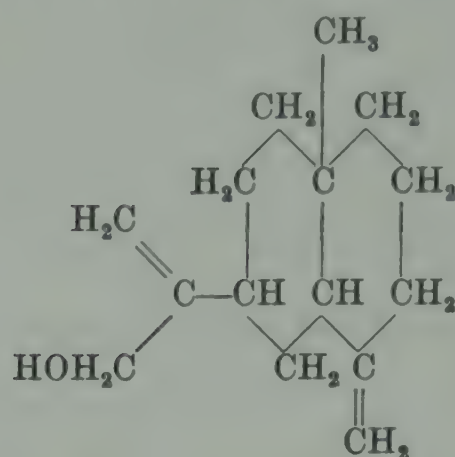
From *Eucalyptus Globulus*, in addition to eudesmol, a second liquid sesquiterpene alcohol, *globulol*, b.p. $283^\circ/755\text{ mm.}$, $[\alpha]_D - 35.29^\circ$, has been separated.[†] This alcohol, as well as the sesquiterpene constituents of the oil, unlike eudesmol, are derivatives of cadalene.[‡] It is of interest that sesquiterpene derivatives of both the naphthalene types should occur in the same oil.

* Semmler and Risse, *Ber.* 1913, **46**, 2304.

† Schimmel's Report, 1904, **1**, 46; Semmler and Tobias, *Ber.* 1913, **46**, 2030.

‡ Ruzicka, Pontalti and Balas, *Helv. Chim. Acta*, 1923, **6**, 861.

SESQUIBENIHIOL



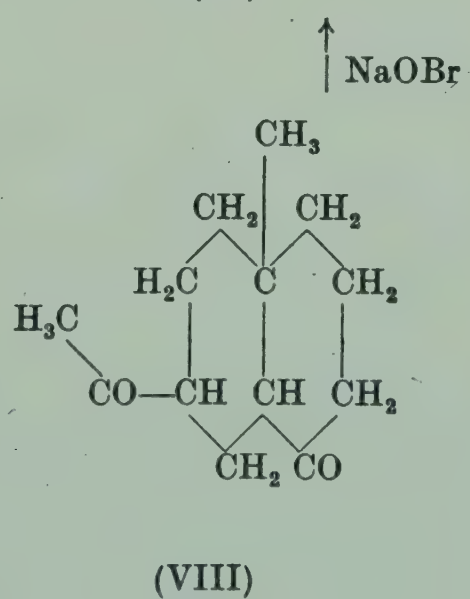
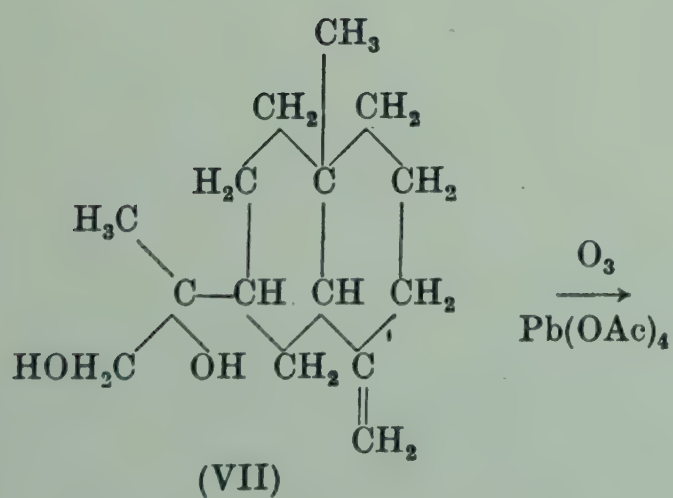
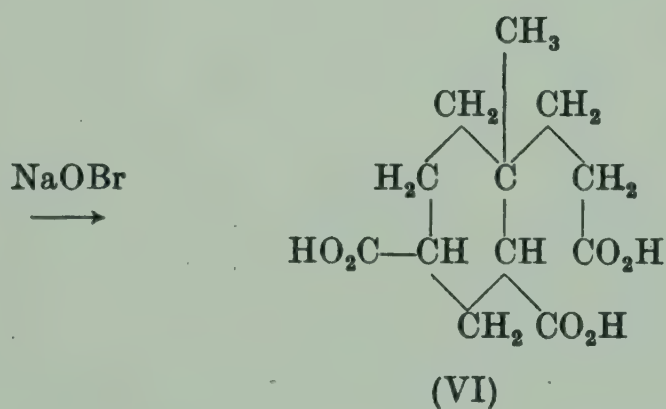
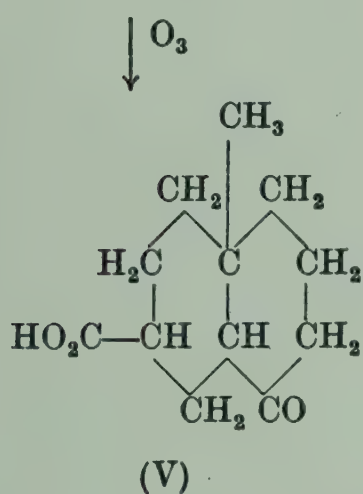
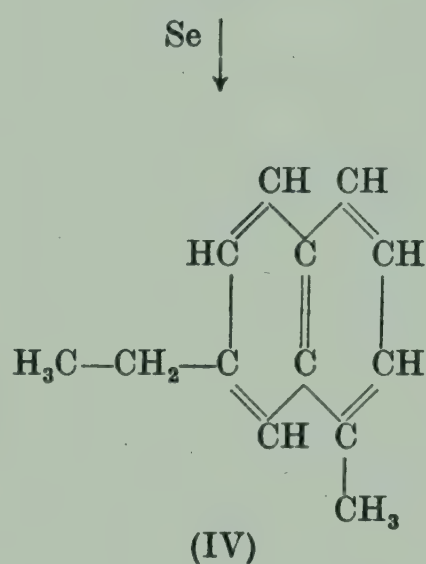
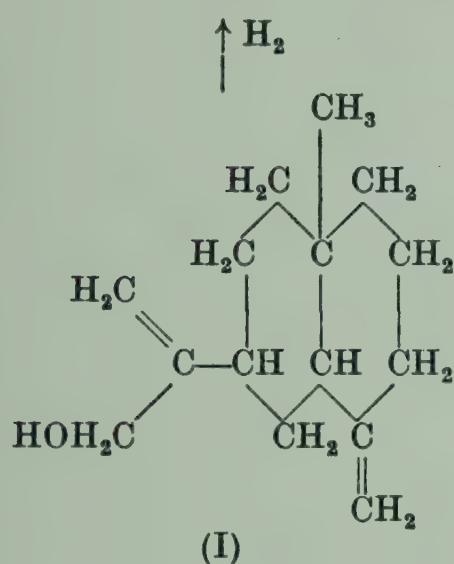
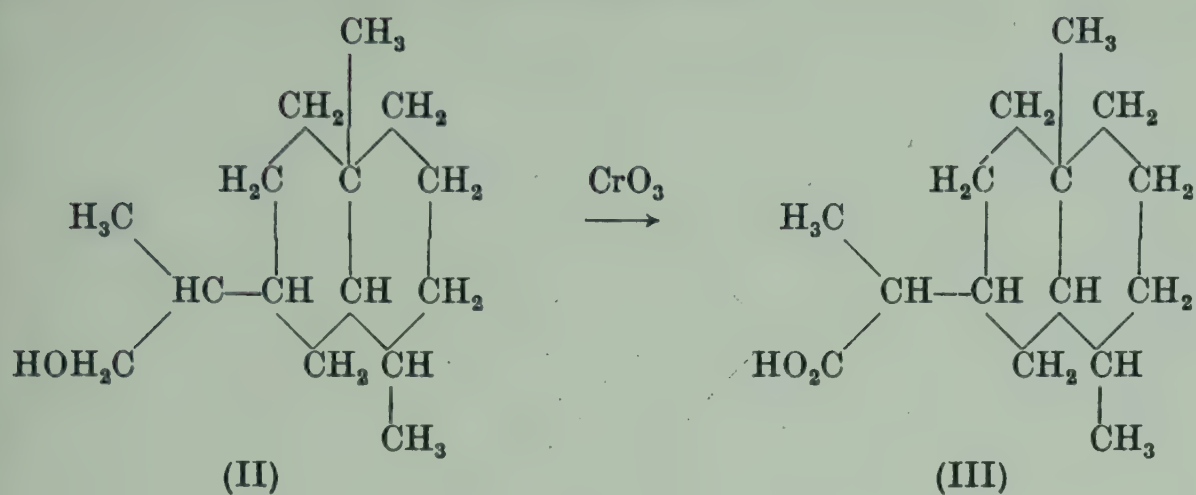
From the essential oil of *Chamaecyparis formosensis* Katsura* separated, in addition to the hydrocarbon sesquibenihiene (see p. 37), a primary alcohol, *sesquibenihiol*, $C_{15}H_{24}O$, b.p. $137^{\circ}/3$ mm., $d_4^{18^{\circ}}$ 0.9977, n_D 1.522, $[\alpha]_D + 8.84^{\circ}$, and a glycol, *sesquibenihiol*, $C_{15}H_{26}O_2$, m.p. $120-130^{\circ}$, $[\alpha]_D^{19^{\circ}} - 36.02^{\circ}$.

Sesquibenihiol is most probably represented by (I). The presence of a primary alcohol group in the side chain and of two ethylenic linkages was proved by its catalytic hydrogenation to *tetrahydrosesquibenihiol*, $C_{15}H_{28}O$ (II), yielding on oxidation with chromic acid a *tetrahydro-acid*, $C_{14}H_{25}.CO_2H$ (III). Support for the structure assigned to this acid was obtained by its dehydrogenation with selenium to 1-*methyl-7-ethylnaphthalene* (IV).

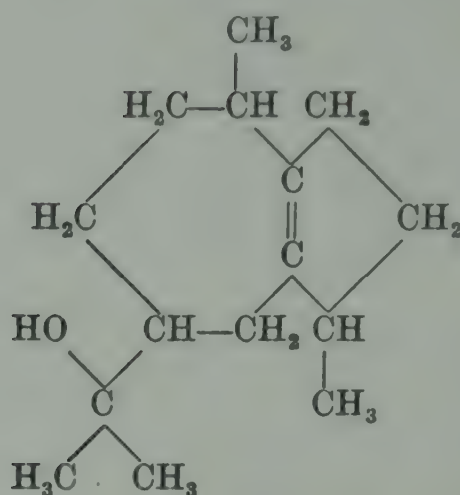
Evidence for the position of the two ethylenic linkages was furnished by the ozonolysis of the alcohol when formaldehyde and a *keto-monocarboxylic acid*, $C_{12}H_{18}O_3$ (*semicarbazone* of *methyl ester*, m.p. $235-237^{\circ}$) were obtained. This acid must be (V) since, on reduction with sodium and alcohol, followed by selenium dehydrogenation it gave naphthalene, whilst on oxidation with sodium hypobromite the *tricarboxylic acid*, $C_{12}H_{18}O_6$, m.p. 189° (VI), was formed. This acid was identical with the acid obtained by the oxidation of α - and β -selinenes (see p. 33).

The glycol, *sesquibenihiol*, is most probably (VII), since it readily yields a hydrogen phthalate, whilst on oxidation with ozone followed by lead tetra-acetate formaldehyde and a *diketone*, $C_{13}H_{20}O_2$ (VIII), were obtained. Further evidence in support of the structures assigned to (VII) and (VIII) was furnished by the oxidation of the latter with sodium hypobromite to the *tricarboxylic acid* (VI).

* *J.C.S. Japan*, 1942, **63**, 1465, 1477.



GUAIIOL



From guaiacum wood oil, which is obtained from the tree *Bulnesia Sarmienti* Lorentz, Schimmel and Co.* separated a crystalline sesquiterpene alcohol, *guaiol*, $C_{15}H_{26}O$, which was obtained later by Baker and Smith† from the oil of *Callitris glauca*. It is probable that the sesquiterpene alcohol, *shairol*, from the roots of *Ferula pyramidata*,‡ is identical with guaiol, and it is possible that the sesquiterpene alcohol isolated by Eyken§ from *Gonystylus Miquelianus* is also substantially guaiol.

Guaiol crystallises in prisms, m.p. 93° , b.p. $147-148^{\circ}/9$ mm., $d_{20}^{100^{\circ}} 0.9074$, $n_D^{100^{\circ}} 1.4716$, $[\alpha]_D -29.8^{\circ}$ (in alcohol). The constitution of guaiol has only recently been completely elucidated, although a number of its more important degradation products were known previously. On dehydrogenation with sulphur, guaiol gave a blue azulene, *S-guaiazulene*, b.p. $164^{\circ}/11$ mm., $d_4^{18^{\circ}} 0.9759$,|| *trinitrobenzoate*, m.p. 151.5° , *picrate*, m.p. $122.5-123.5^{\circ}$, *styphnate*, m.p. $105-106^{\circ}$, *trotylate*, m.p. 89° ,¶ which has been shown to be represented by (I) (see p. 7). The structure (II), now accepted for guaiol, is based essentially on its dehydrogenation to this azulene, the positions of the ethylenic linkage and the hydroxyl group being supplied by the following evidence.

The oxygen atom in guaiol was shown to be present as a tertiary alcohol group by (i) the difficulty of acetylation,** (ii) the

* Schimmel's Report, 1892, II, 42.

† Pines of Australia, 1910, pp. 63, 118.

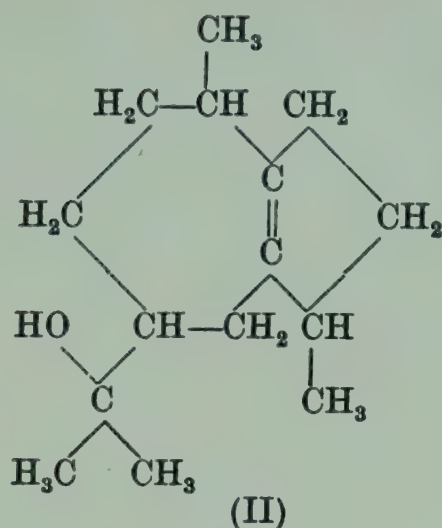
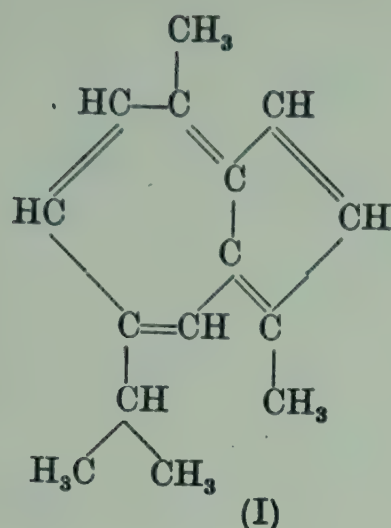
‡ Kirialow, *J. Appl. Chem. (U.S.S.R.)*, 1941, 13, 579; *J. Gen. Chem. (U.S.S.R.)*, 1943, 13, 145; 1950, 20, 188.

§ *Rec. trav. chim.* 1906, 25, 44.

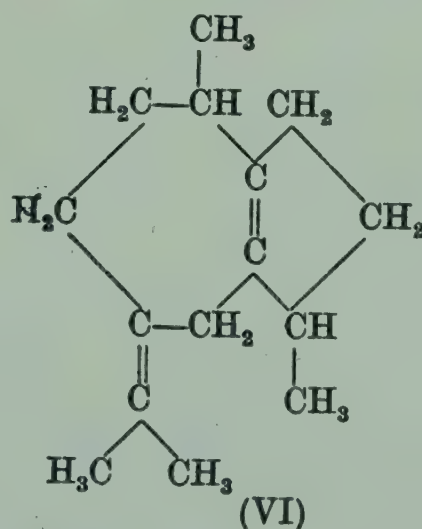
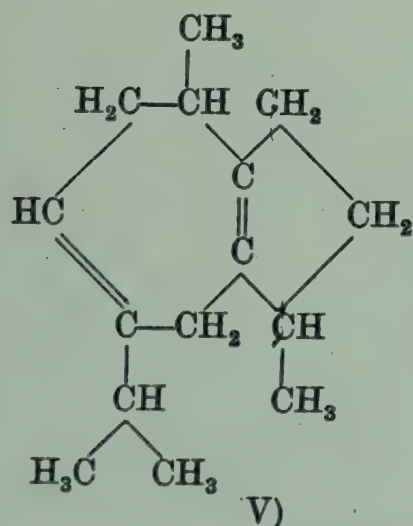
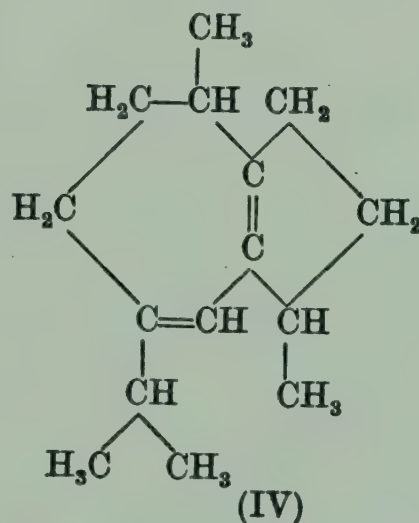
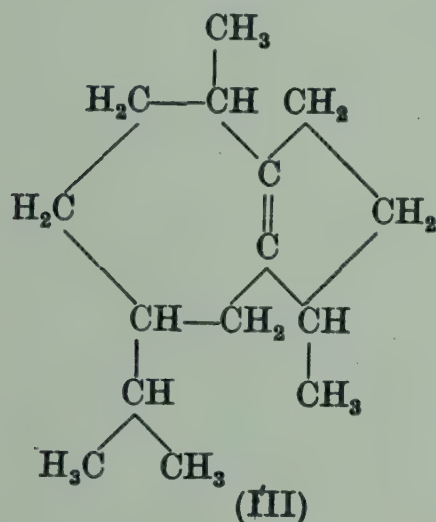
|| Ruzicka and Rudolph, *Helv. Chim. Acta*, 1926, 9, 118.

¶ Pfau and Plattner, *ibid.* 1936, 19, 858.

** Gandurin, *Ber.* 1908, 41, 4359.



non-reactivity with phthalic anhydride even at 130° ,* (iii) reduction by heating with zinc dust at 220° to a hydrocarbon *dihydroguaiene* (III), $C_{15}H_{26}$, b.p. $122^{\circ}/11$ mm., $d_4^{20^{\circ}}$ 0.8914, $n_D^{20^{\circ}}$ 1.4982, $[\alpha]_D^{18.5^{\circ}}$ -26.65° ,† and (iv) the comparative ease of dehydration of guaiol to a hydrocarbon or mixture of hydrocarbons called *guaiene*, probably (IV), (V) and (VI), b.p. $128-130^{\circ}/12$ mm., $d_4^{19^{\circ}}$ 0.9115, $n_D^{20^{\circ}}$ 1.5022, α_D -16.8° .‡

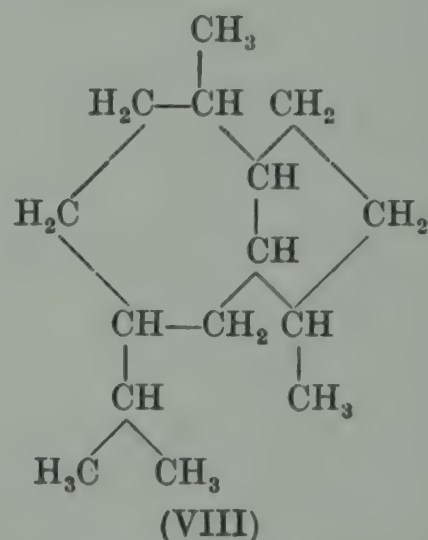
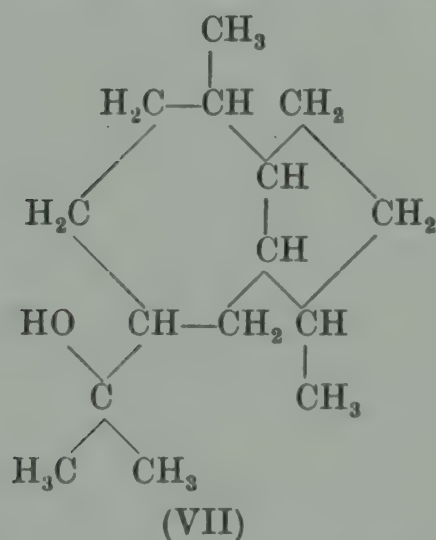


* Ruzicka, Pontalti and Balas, *Helv. Chim. Acta*, 1923, 6, 862.

† Gandurin, *Ber.* 1908, 41, 4361.

‡ Wallach, *Annalen*, 1894, 279, 395; Gadamer and Amenomiya, *Arch. Pharm.* 1903, 241, 22; Gandurin, *Ber.* 1908, 41, 4359; Ruzicka, Pontalti and Balas, *loc. cit.*

Although it has been stated that guaial can be readily hydrogenated,* the careful experiments of Plattner and Lemay† suggest that this is not the case. By the hydrogenation of the alcohol at 110° under a pressure of 100 atmospheres, using Raney nickel as catalyst, dihydroguaial (VII), m.p. $78-79^{\circ}$, $[\alpha]_D -54^{\circ}$ (in acetone) was obtained. This alcohol is accompanied by at least two other stereoisomeric alcohols which have not, however, been obtained pure. These experiments suggest that the ethenoid linkage in guaial is most probably situated between two fully substituted carbon atoms as in formula (II) and that guaial is bicyclic. It is somewhat difficult to reconcile these results with the claim of Semmler and Risse‡ to have prepared *tetrahydroguaiene* (VIII), b.p. $118-119^{\circ}/7$ mm., $d^{20}_{20} 0.8806$, $n_D 1.4784$, $[\alpha]_D +10.31^{\circ}$, by hydrogenation of guaial in acetic acid solution using a platinum black catalyst; it is to be assumed that an especially active catalyst was employed.



Valuable evidence as to the structure of guaial and more especially as to the position of the hydroxyl group has been obtained by Plattner and his collaborators§ from a study of the reactions of dihydroguaial. Dihydroguaial was dehydrated by treatment with either acetic anhydride, aluminium oxide or potassium bisulphate, or by pyrolysis of the benzoate, to furnish a mixture of hydrocarbons of variable composition best designated *isodihydroguaiene*, b.p. $123-124^{\circ}/11$ mm., $[\alpha]_D -59^{\circ}$ (in alcohol). When this mixture of hydrocarbons, consisting

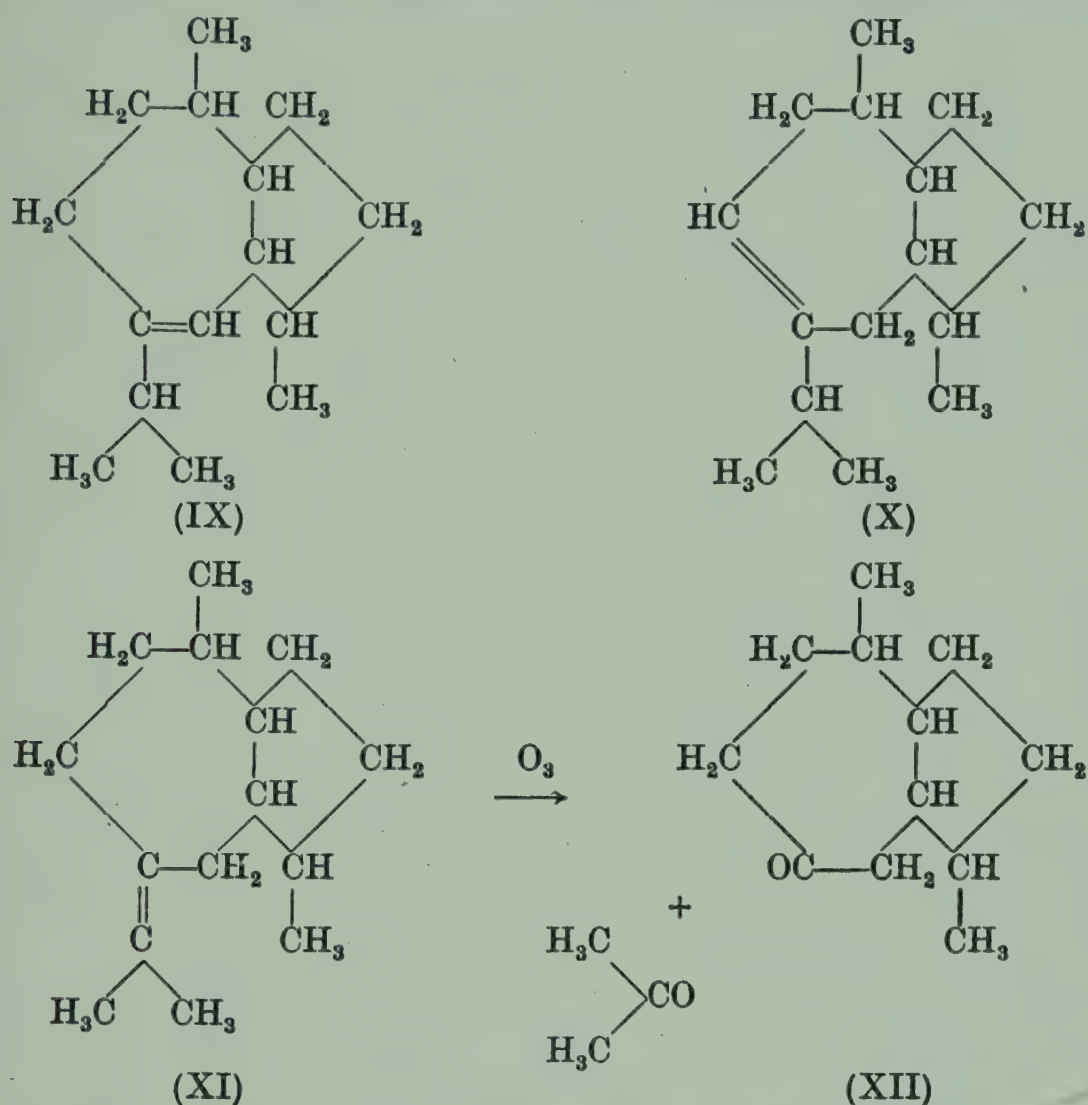
* Ruzicka and Haagen-Smit, *Helv. Chim. Acta*, 1931, **14**, 1104.

† *Ibid.* 1940, **23**, 897.

‡ *Ber.* 1913, **46**, 2305.

§ Plattner and Lemay, *Helv. Chim. Acta*, 1940, **23**, 897; Plattner and Magyar, *ibid.* 1942, **25**, 581.

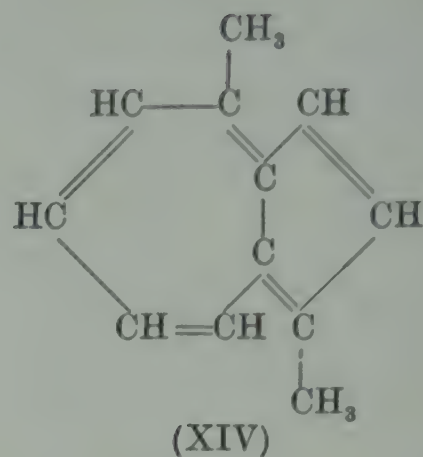
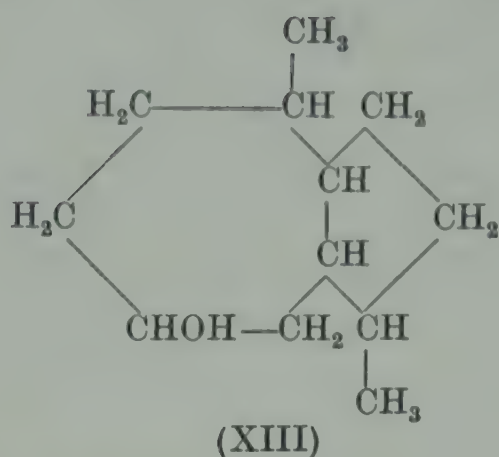
probably of (IX), (X) and (XI), was ozonised, roughly equimolecular amounts of acetone and a *ketone*, $C_{12}H_{20}O$ (XII), b.p. $130-131^{\circ}/11$ mm., $d_4^{20^{\circ}} 0.9720$, $n_D^{20^{\circ}} 1.4879$, $[\alpha]_D -107^{\circ}$ (in alcohol), *semicarbazone*, m.p. 206° were obtained, derived from the (XI) present in the mixture. The other products from the



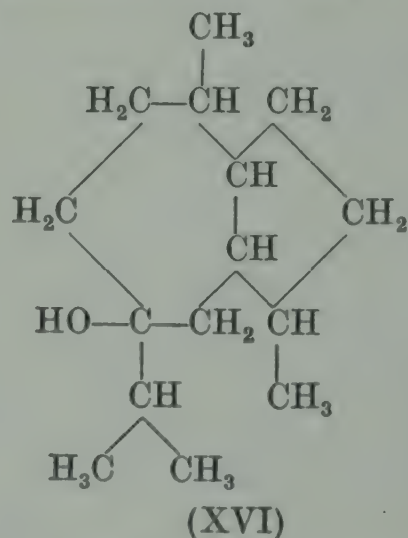
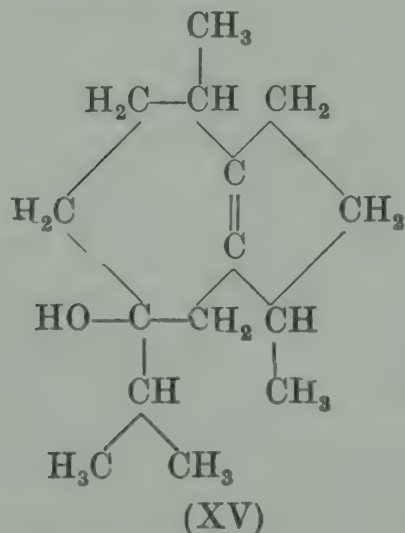
ozonolysis consisted of a mixture of *keto-aldehydes* and *keto-aldehyde peroxides* which were not isolated in a state of purity, and were presumably derived from (IX) and (X). Conclusive proof of the carbon skeleton in (XII) was obtained by its reduction in the presence of Raney nickel to the secondary *alcohol* (XIII), b.p. $130-134^{\circ}/10$ mm., which, after dehydration with potassium bisulphate followed by dehydrogenation with sulphur gave 1:4-dimethylazulene (XIV), *trinitrobenzoate*, m.p. $177-178^{\circ}$, *picrate*, m.p. $142-143^{\circ}$, identical with the synthetic hydrocarbon.*

The isolation of the ketone (XII), together with acetone, suggested that the tertiary hydroxyl group in guaiol must be situated either in the *isopropenyl* side chain as in (II) or in the

* Plattner and Lemay, *loc. cit.*

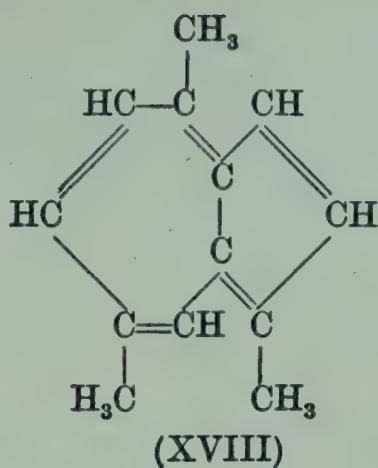
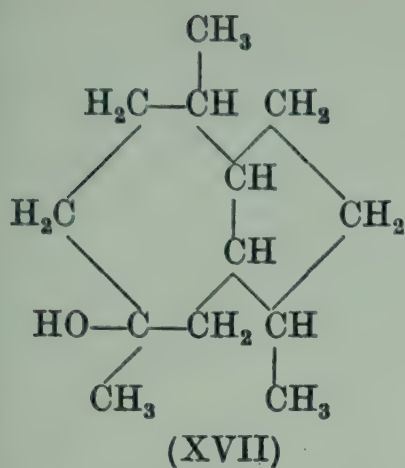


ring as indicated in (XV). Confirmation that the formulation as in (II) was correct and also, incidentally, of the position of the carbonyl group in the ketone (XII), was furnished by the investigations of Plattner and Magyar.* By the action of *isopropyl* magnesium iodide on the ketone (XII) they attempted the synthesis of the alcohol (XVI). The latter substance could not, however, be isolated since, during the reaction, dehydration occurred with the formation of the mixture of hydrocarbons, *isodihydroguaiane* (see p. 158). The "synthetic" hydrocarbons gave on dehydrogenation with sulphur, *S-guaiazulene* (I) (p. 157). It would be anticipated that the alcohol (XVI) would be less stable than (II) or (VII), in agreement with experiment.

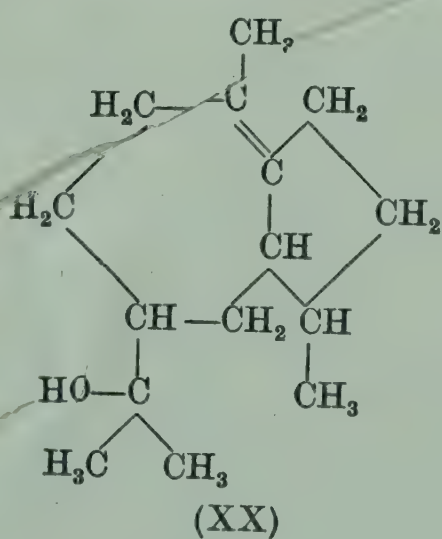
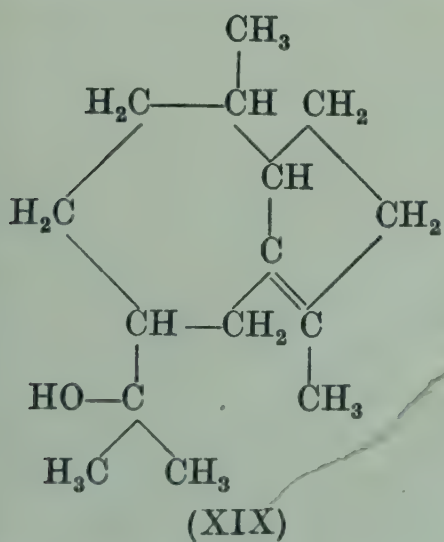


When the ketone (XII) was treated with methyl magnesium iodide the *alcohol* (XVII), m.p. 83° , $[\alpha]_D -10^{\circ}$ (in hexane), was obtained in excellent yield. On dehydration with potassium bisulphate, followed by dehydrogenation with sulphur, 1:4:7: -*trimethylazulene* (XVIII), *trinitrobenzoate*, m.p. $177-178^{\circ}$, was obtained, thus leaving no doubt as to the position of the carbonyl group in the parent ketone.

* *Helv. Chim. Acta*, 1942, 25, 581.



Whilst the experiments on the hydrogenation of guaiol referred to above indicated that the ethylenic linkage in the alcohol was situated between two tertiary carbon atoms, they did not distinguish between the three possible formulae (II), (XIX) and (XX). Proof that the ethylenic linkage was situated as in (II) was provided by Plattner and Magyar,* who reinvestigated the properties of the saturated *dihydroxyketone*, $C_{15}H_{26}O_3$, m.p. $220-221^\circ$, $[\alpha]_D + 50^\circ$ (in alcohol), which had been prepared by Semmler and Mayer[†] by oxidation of the alcohol with potassium permanganate and by Ruzicka and Haagen-Smit[‡] by its ozonolysis. This hydroxy-ketone, originally considered to be an oxide owing to the non-reactivity of its carbonyl group, was very readily dehydrated either by digestion with dilute alkali or with glacial acetic acid, to yield an $\alpha:\beta$ -unsaturated *ketone*, $C_{15}H_{22}O$, b.p. $140-143^\circ/14$ mm., $d_4^{20} 0.9935$, $n_D^{20} 1.5298$, $[\alpha]_D + 127.9^\circ$ (in alcohol). This ketone did not react with the usual carbonyl reagents but its absorption spectrum, λ max. 265 m μ , $\log \epsilon 4.24$

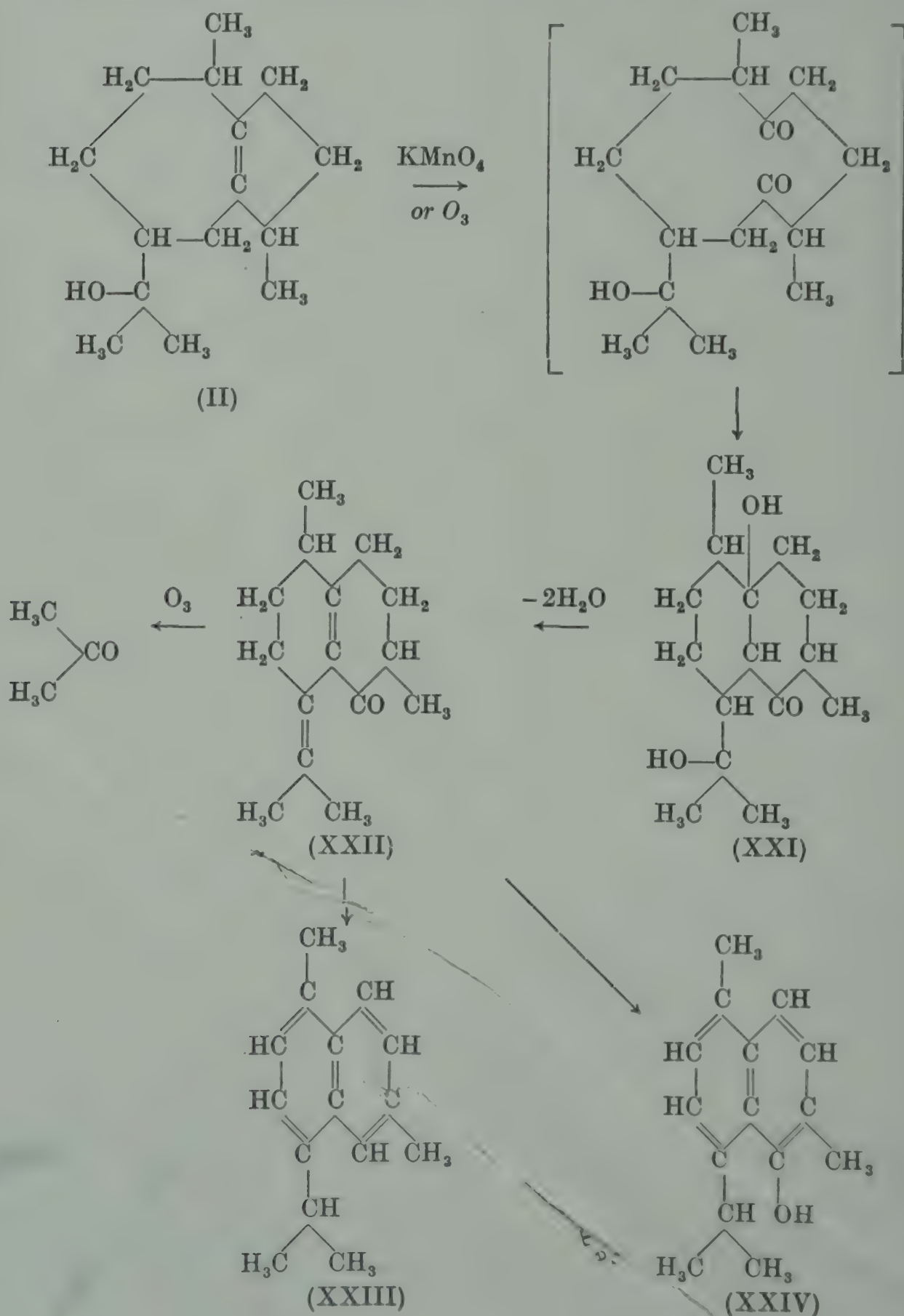


* *Ibid.* 1941, 24, 191.

[†] *Ber.* 1912, 45, 1391; compare Trikojus and White, *J. Proc. Roy. Soc. New South Wales*, 1935, 68, 177.

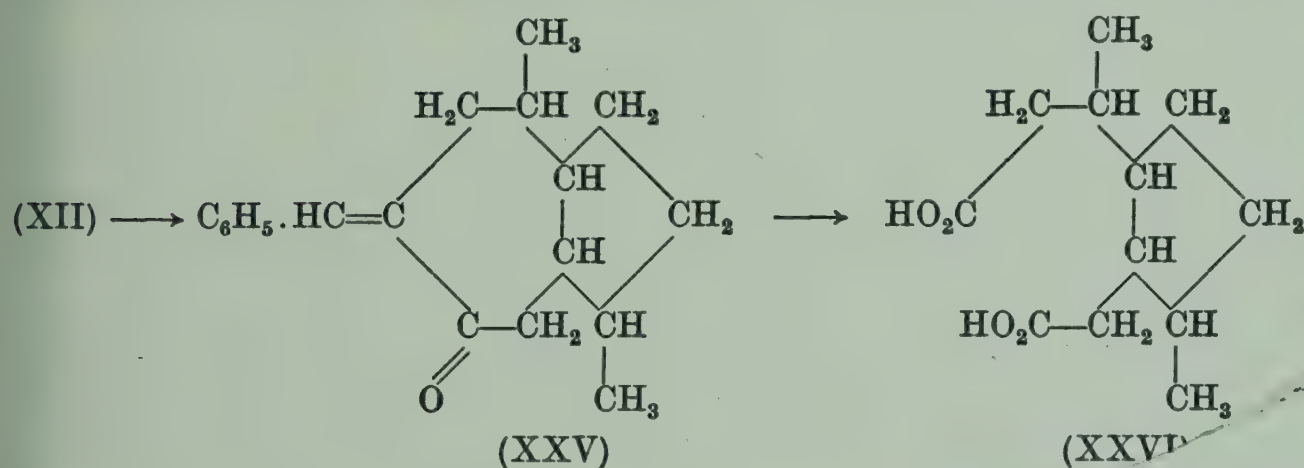
[‡] *Loc. cit.*

(in alcohol) showed that it possessed an $\alpha:\beta$ -unsaturated keto-group. The presence of a carbonyl group in the parent dihydroxy-ketone was inferred also from a study of its absorption spectrum, and its ready dehydration suggested that it was a β -hydroxy-ketone. On the assumption that (II) correctly represents guaio then the dihydroxy-ketone would be (XXI), formed from the



primary oxidation product by ring enlargement and contraction. The unsaturated ketone would then be (XXII). This formula for the ketone was confirmed by its conversion (a) into cadalene (XXIII) on heating in a sealed tube with palladised charcoal, and (b) into 2:5-dimethyl-8-isopropyl-1-naphthol (XXIV) by heating with the same reagent in an open tube. Further, the presence of the isopropylidene group was proved by the formation of acetone on ozonolysis. If guaiol had been represented by either (XIX) or (XX) its conversion into cadalene would not have been possible.

The oxidation of dihydroguaiol (VII) with chromic acid provided a more convenient route to the ketone (XII) (p. 159). A further product of the oxidation was a *dicarboxylic acid*, $C_{12}H_{20}O_4$, m.p. 186–187°, $[\alpha]_D \pm 0$ (in alcohol), $+1.5^\circ$ (in alcoholic potassium hydroxide). This acid can be prepared also by ozonolysis of the *monobenzylidene* derivative, m.p. 149°, $[\alpha]_D +124.1^\circ$ (in alcohol) of the ketone (XII). Since this derivative is most probably represented by (XXV) the acid must be (XXVI).



Although guaiol, on dehydrogenation with sulphur, yields S-guaiazulene (see p. 156), a different azulene *Se-guaiazulene*, *picrate*, m.p. 114–115°, *stypnate*, m.p. 98–99° is obtained on dehydrogenation with selenium.* *Se-guaiazulene* is violet in colour and, although its structure has not been determined with certainty, it probably has substituents at the 2:4:7 positions in the azulene skeleton.†

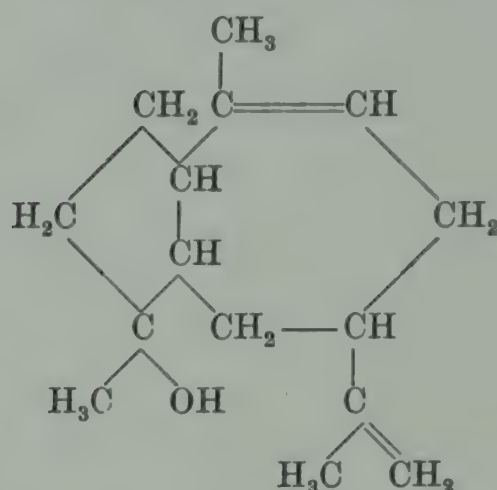
Guaiol can be conveniently characterised by its physical constants, by the preparation of the 3:5-dinitrobenzoate, m.p. 137–

* Ruzicka and Haagen-Smit, *Helv. Chim. Acta*, 1931, 14, 1104.

† Plattner, *ibid.* 1941, 24, 283 E; compare, however, Pfau and Plattner, *ibid.* 1936, 19, 858; Birrell, *J. Amer. C.S.* 1934, 56, 1248; 1935, 57, 893.

137.5°, and by reduction to dihydroguaiol, 3:5-dinitrobenzoate, m.p. 150°, $[\alpha]_D - 14.2^\circ$. The dihydroxyketone (XXI) and its dehydration product (XXII) mentioned above are also characteristic and easily prepared derivatives.

PARTHENIOL

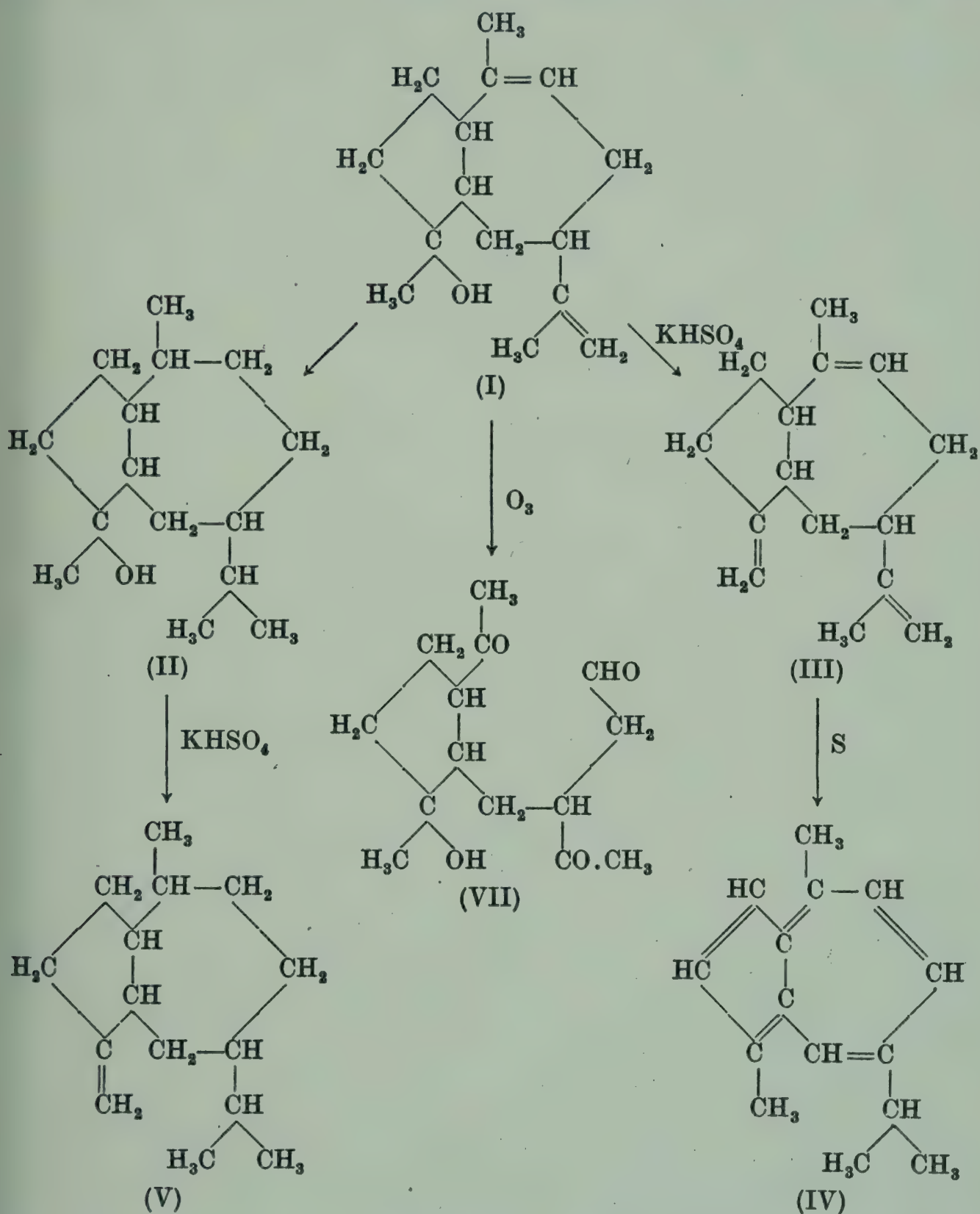


The bicyclic sesquiterpene alcohol, *partheniol*, $C_{15}H_{24}O$, m.p. 127–128°, $[\alpha]_D^{26^\circ} + 116.5^\circ$ (in chloroform), occurs as the *cinnamate*, $C_{24}H_{30}O_2$, m.p. 125–126°, in guayule (*Parthenium argentatum* Gray). It is most conveniently isolated from guayule resin, a by-product in the refining of guayule rubber.* The constitution of partheniol (I) has been elucidated by Haagen-Smit and Fong.† Partheniol contains two olefinic linkages as shown by the fact that, on catalytic hydrogenation in acid solution, it gave the saturated *tetrahydropartheniol* (II), $C_{15}H_{28}O$, b.p. 70–85°/0.01 mm., $d_4^{25.4^\circ} 0.9342$, $n_D^{25^\circ} 1.4820$. It must therefore be bicyclic. The oxygen atom is present as a tertiary alcoholic grouping, since partheniol could not be esterified and yet was readily dehydrated by potassium bisulphate to the triply unsaturated *anhydropartheniol* (III), $C_{15}H_{22}$, b.p. 60–65°/0.1 mm., $d_4^{23.6^\circ} 0.9194$, $n_D^{26^\circ} 1.1512$. Dehydrogenation of this hydrocarbon with sulphur afforded *S-guaiazulene* (IV), $C_{15}H_{18}$, *picrate*, m.p. 120–121°, *trinitrobenzene adduct*, m.p. 150–151°, *trinitrotoluene adduct*, m.p. 88–89°, previously obtained from guaiol (p. 156). This experiment characterises the carbon skeleton of partheniol and leaves undecided only the positions of the two olefinic linkages

* Alexander, *Ber.* 1911, **44**, 2320; Walter, *J. Amer. C.S.* 1944, **66**, 419; Haagen-Smit and Fong, *ibid.* 1948, **70**, 2075.

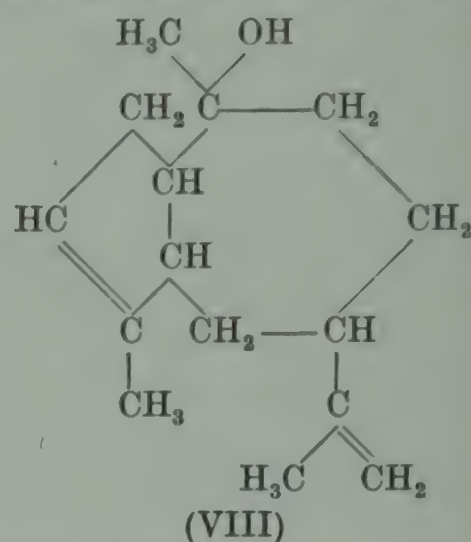
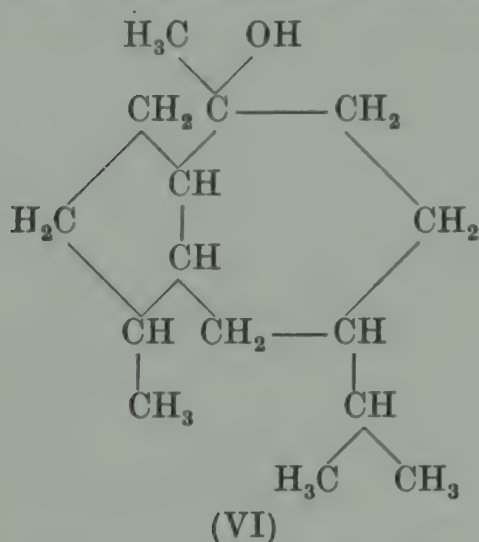
† *Loc. cit.*

and of the tertiary hydroxyl group. These structural features were established in the following way. Dehydration of *tetrahydropartheniol* afforded *anhydrotetrahydropartheniol* (V), $C_{15}H_{26}$,

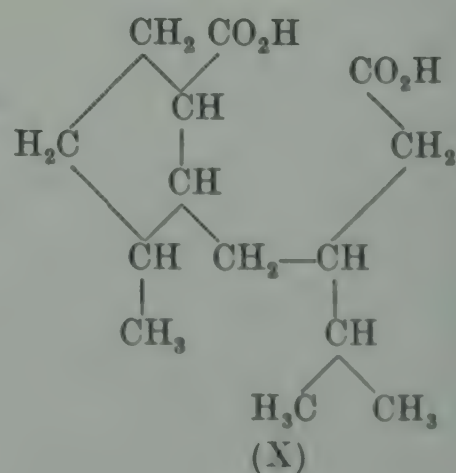
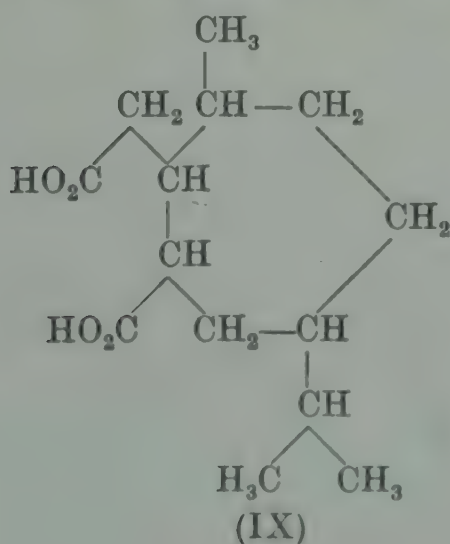


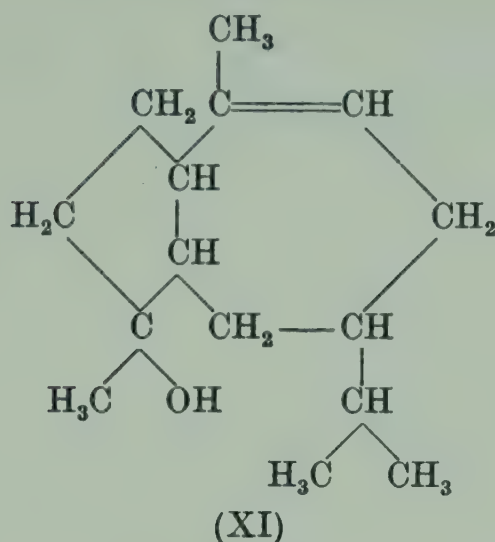
b.p. $59-60^{\circ}/0.02$ mm., $d_4^{25^{\circ}}$ 0.9025, $n_D^{25^{\circ}}$ 1.4880, which on ozonolysis gave formaldehyde but no acetone. This was taken to mean that tetrahydropartheniol must be either (II) or (VI). The correctness of this deduction was proved by a study of the ozonolysis products of partheniol itself. These included formaldehyde and

a *hydroxy-aldehyde* (VII), $C_{14}H_{22}O_4$, b.p. $98-100^\circ/0.6$ mm., $d_4^{24^\circ} 1.0624$, $n_D^{24^\circ} 1.4762$, which contained two methyl ketone groupings. The formaldehyde in this ozonolysis must have come from an *isopropenyl* group and the other methyl group must be adjacent to an olefinic linkage in order to explain the production of both a $CH_3.CO-$ and an aldehyde group. The facts can only



be explained on the basis of formulae (I) or (VIII) for partheniol. Both these formulae explain the observed absence of conjugation in partheniol and anhydropartheniol and it was possible to distinguish between them in the following way: ozonolysis of anhydropartheniol, which must contain other double bond isomers besides (V), followed by hypobromite oxidation, furnished a dicarboxylic acid, $C_{14}H_{24}O_4$, b.p. $190-200^\circ/0.1$ mm., which must be represented by (IX) or (X) depending upon the correctness of formulae (II) or (VI) for tetrahydropartheniol. A decision in favour of (IX) was reached since the dicarboxylic acid gave an *anhydride*, $C_{14}H_{22}O_3$, b.p. $200-210^\circ/0.01$ mm., on heating at 240° with acetic anhydride and not a ketone as would have been expected from (X).

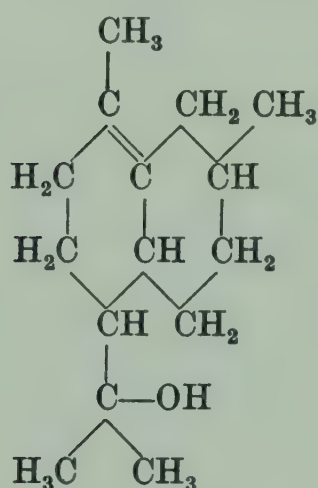




Partheniol may be characterised by the formation of the 3:5-dinitrobenzoate, m.p. 143–144°, or the p-phenylazobenzoate, m.p. 163–164°.

Hydrogenation of partheniol in alcoholic solution using Raney nickel gave *dihydropartheniol*, $C_{15}H_{26}O$, probably (XI), b.p. 92–102°/0.1 mm., $d_4^{23.6^\circ}$ 0.9614, $n_D^{26^\circ}$ 1.5035.

CAROTOL

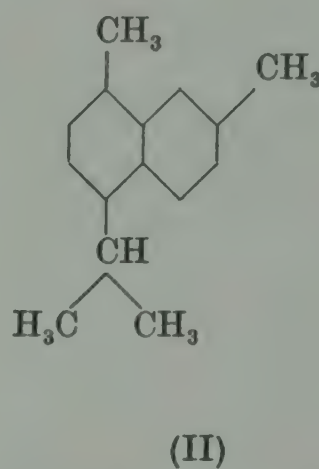
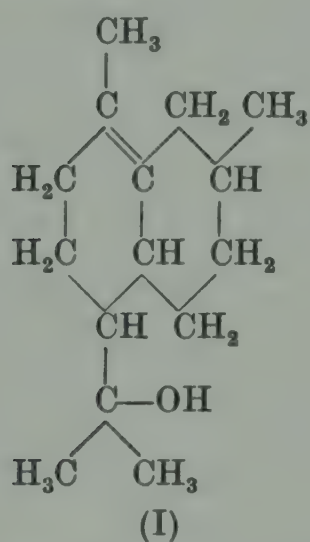


The sesquiterpene alcohol, *carotol*, $C_{15}H_{26}O$, b.p. 97–98°/0.25 mm., $d_4^{20^\circ}$ 0.9702, $n_D^{20^\circ}$ 1.4997, $[\alpha]_D^{18^\circ}$ + 6.9° (in alcohol), was first isolated by Asahina and Tsukamoto* from the essential oil of *Daucus Carota* L. It was later investigated by Šorm and Urbánek,† who were able to determine its structural formula as shown in (I). Šorm and Urbánek found that on catalytic hydrogenation the saturated *dihydrocarotol*, $C_{15}H_{28}O$, b.p. 131–133°/11 mm., $d_4^{20^\circ}$ 0.9541, $n_D^{20^\circ}$ 1.4900, $[\alpha]_D^{18^\circ}$ + 3.1° (in alcohol), was produced. The presence of only one ethylenic linkage, and hence two rings,

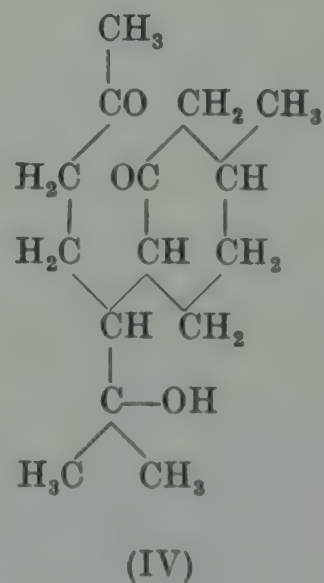
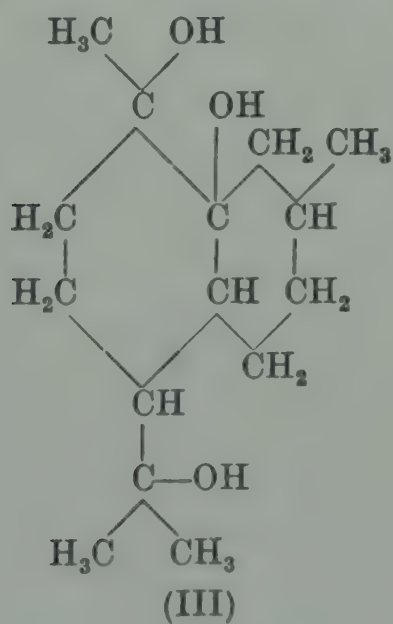
* *J. Pharm. Soc. Japan*, 1925, No. 525, p. 961.

† *Coll. Czech. Chem. Comm.* 1948, 13, 49, 420; 1949, 14, 98.

implied by this experiment, was confirmed by the formation of a crystalline *carotol oxide*, $C_{15}H_{26}O_2$, m.p. 118° , $[\alpha]_D^{18} - 24.0^\circ$ (in alcohol), on treatment with perphthalic acid. The dehydrogenation of carotol with palladised charcoal* gave very interesting results. Besides a small amount of unidentified azulene the main product of the reaction was an aromatic *hydrocarbon*, $C_{15}H_{18}$, m.p. 60° , b.p. $90^\circ/0.14$ mm., *picrate* m.p. 91° , *styphnate* m.p. 120° , identical with 1:7-dimethyl-4-isopropylnaphthalene (II). This implied that the carbon skeleton of carotol was of a novel type different from that of either the cadalene or eudalene groups of sesquiterpenes.



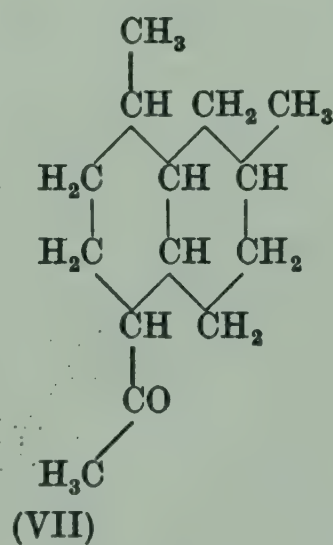
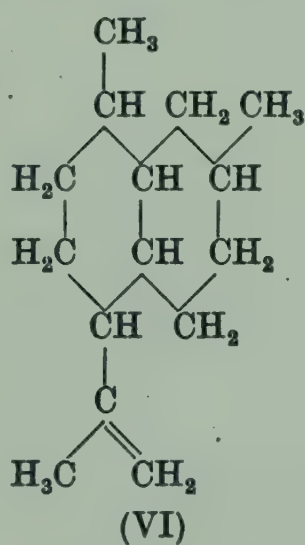
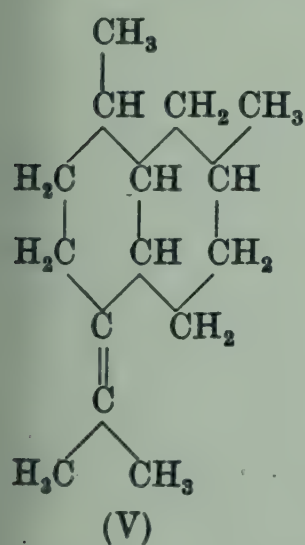
On oxidation with potassium permanganate carotol afforded a crystalline *triol* (III), $C_{15}H_{28}O_3$, m.p. 142° , $[\alpha]_D^{18} - 1.4^\circ$ (in alcohol), which on further oxidation with periodic acid or lead tetra-acetate gave a *diketone*, $C_{15}H_{26}O_3$, m.p. 98° , $[\alpha]_D^{18} + 12.6^\circ$ (in alcohol). One of the ketonic oxygens in this substance was



* Šorm and Urbánek, *loc. cit.*

present as a methyl ketone for iodoform was obtained on oxidation with hypoiodite. This evidence can only be reconciled with the di-tertiary position for the ethylenic linkage indicated in the formula (IV) for the derived diketone.

The oxygen atom in carotol was recognised to be present as a tertiary alcoholic grouping because of its unreactive character towards acylating agents and its ease of elimination. Thus when carotol was treated with formic acid it was smoothly dehydrated to a mixture of *hydrocarbons*, $C_{15}H_{24}$, b.p. $71-73^{\circ}/0.48$ mm., $d_4^{20^{\circ}}$ 0.9140, $n_D^{20^{\circ}}$ 1.5002, $[\alpha]_D^{18^{\circ}} + 6.2^{\circ}$ (in alcohol). Dihydrocarotol was dehydrated in a similar manner to give a mixture of *hydrocarbons*, $C_{15}H_{26}$, presumably (V) and (VI), b.p. $58-59^{\circ}/0.17$ mm., $d_4^{20^{\circ}}$ 0.8804, $n_D^{20^{\circ}}$ 1.4823, $[\alpha]_D^{18^{\circ}} + 2.0^{\circ}$ (in alcohol), which on ozonolysis afforded acetone, formaldehyde and formic acid. The tertiary alcoholic grouping must therefore be attached as indicated in the complete structural formula (I) for carotol. This conclusion was confirmed by oxidation of dihydrocarotol with chromic acid. Besides the same hydrocarbon mixture as was obtained on formic acid dehydration a small amount of a ketonic *substance*, $C_{14}H_{24}O$, presumably (VII), b.p. $86-87^{\circ}/0.2$ mm., *semicarbazone*, $C_{15}H_{27}ON_3$, was formed.



The properties of carotol oxide are in agreement with those recorded by Richter* for *daucol*, $C_{15}H_{26}O_2$, obtained by him from the same essential oil and the identity of these substances may be taken as established.

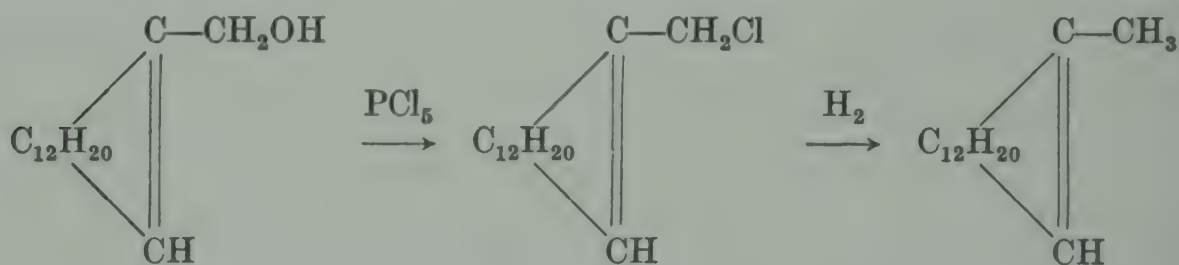
* *Arch. Pharm.* 1909, 247, 391.

D. TRICYCLIC ALCOHOLS

Prim.-CEDRENOL

The alcohol, *prim.-cedrenol*, $C_{15}H_{24}O$, was found by Semmler and Mayer* to be present in the higher boiling fractions of cedar wood oil. The alcohol was separated by treating the fraction of the oil, b.p. $152-170^{\circ}/7$ mm., with phthalic anhydride in benzene solution. On hydrolysis of the hydrogen phthalate, a viscid oil was obtained, which was further purified by conversion into the acetate. *Prim.-cedrenol acetate* boils at $168-169^{\circ}/9$ mm., d^{20}_{20} 1.0168, n^{20}_D 1.5021, $\alpha_D - 2^{\circ}$, and gives, on hydrolysis with alkali, *prim.-cedrenol*, b.p. $166-169^{\circ}/9.5$ mm., d^{20}_{20} 1.0083, n^{20}_D 1.5212.

Prim.-cedrenol bears the same relationship to cedrene as myrtenol does to α -pinene. When the alcohol is treated with phosphorus pentachloride in light petroleum solution the corresponding *chloride*, b.p. $150-165^{\circ}/10$ mm., d^{20}_{20} 1.001, is obtained, and this, on reduction, yields cedrene. The relationship of cedrenol to cedrene is therefore shown by the scheme:



Prim.-cedrenol has also been obtained by the selenium dioxide oxidation of cedrene (p. 77), but the more recently recorded physical constants are not in good agreement with those of Semmler and Mayer quoted above.

CEDROL

The crystalline sesquiterpene alcohol, *cedrol*, $C_{15}H_{26}O$, which is known also as *cedar camphor* and *cypress camphor*, occurs not only in cedar wood oil from *Juniperus virginiana*, but also in cypress oil from *Cupressus sempervirens* L.,† in the oil from *Juniperus chinensis*‡ and in the oil from *Origanum smyrnaeum* L.§

* Ber. 1912, 45, 786.

† Schimmel's Report, 1904, II, 20.

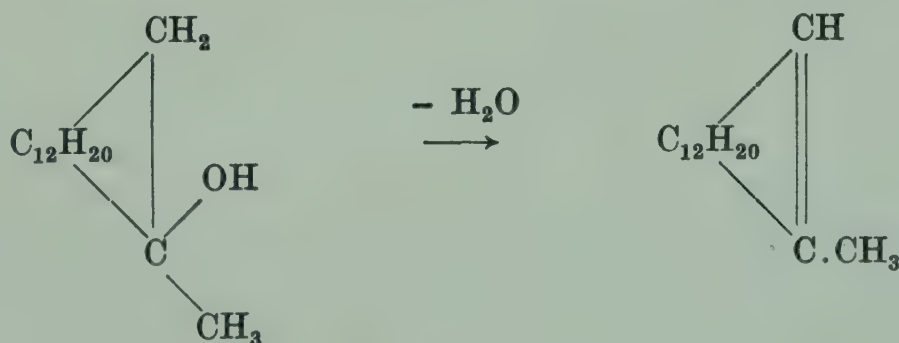
‡ Kondo, J. Pharm. Soc. Japan, 1907, p. 236.

§ Schimmel's Report, 1906, Oct., p. 72.

Cedrol was first isolated and investigated by Walter.* He considered that it had the composition $C_{16}H_{26}O$ and he observed that, on treatment with phosphorus pentoxide, water was eliminated with the formation of a hydrocarbon, *cedrene*, $C_{16}H_{24}$. In reviewing Walter's results, Gerhardt† suggested that his formula was incorrect and that the alcohol had the composition $C_{15}H_{26}O$, and the hydrocarbon, $C_{15}H_{24}$, a conclusion confirmed by subsequent investigations. In 1897 Rousset‡ subjected cedrol to a renewed study. He concluded that it was a tertiary alcohol and he succeeded in preparing an *acetate*, b.p. $157-160^{\circ}/8$ mm., although the yield was small owing to the tendency which cedrol showed to lose water and yield a hydrocarbon. The hydrocarbon is obtained in an excellent yield if cedrol is warmed with formic acid.§

Cedrol crystallises from methyl alcohol in needles, m.p. 86° , b.p. 292° . Whilst there is no doubt of the structural identity of the alcohols separated from the various oils referred to above, they show a marked variation in their optical rotatory power. In a number of cases the alcohol is optically inactive, but as a rule it is *dextrorotatory*, the highest value recorded being $[\alpha]_D + 10.5^{\circ}$ (in chloroform).

Cedrol is undoubtedly a tertiary alcohol; it does not react with phthalic anhydride and, on oxidation with chromic acid, it does not yield either an aldehyde or a ketone, but is dehydrated. The determination of its constitution is dependent upon that of the hydrocarbon, *cedrene* (see p. 75), since, as has been shown by Semmler and Spornitz,|| it gives this hydrocarbon when dehydrated with formic acid. Their relationship is indicated by the formulae:



* *Annalen*, 1841, **39**, 247; 1843, **48**, 35; *Ann. Chim.* 1843 [iii], **1**, 498; 1844 [iii], **8**, 854.

† *Traité*, 1856, iv, 353.

‡ *Bull. Soc. chim.* 1897 [iii], **17**, 485.

§ *Schimmel's Report*, 1897, II, 12.

|| *Ber.* 1912, **45**, 1553.

Cedrol can be identified by the preparation of the *phenylurethane*, m.p. 106–107°, whilst Wienhaus* has described a *chromate*, $(C_{15}H_{25})_2CrO_4$, m.p. 115°, prepared by the action of chromic acid on the alcohol in carbon tetrachloride solution.

In 1912, Semmler and Mayer† made the interesting observation that cedar wood oil does not always yield a crystalline cedrol, but that the sesquiterpene alcohol consists sometimes of an isomeric liquid *alcohol*, b.p. 147–152°/9 mm., d^{20}_D 0.9964, n^{20}_D 1.5131, $\alpha_D + 21.5^\circ$. Like cedrol this alcohol is a tertiary alcohol and, when it is heated with zinc dust at 225–235°, it is converted into a saturated hydrocarbon, *dihydrocedrene*,‡ $C_{15}H_{26}$, b.p. 109–112°/10 mm., d^{20}_D 0.907, n_D 1.4882, $\alpha_D + 37^\circ$ (compare p. 86).

For this new alcohol Semmler and Mayer suggest the name *pseudocedrol*, since it yields on dehydration cedrene and, as has been shown by Kimura,§ it can be converted into cedrol, either by digestion with potassium or by the hydrolysis of its xanthate. According to Bell,|| *pseudocedrol* is obtained when cedrene is treated with mercuric acetate in acetic acid solution.

LEDOL (*LEDUM CAMPHOR*)

Marsh tea oil, which is obtained from the leaves and flowering tips of *Ledum palustre* L., contains a crystalline sesquiterpene alcohol, $C_{15}H_{26}O$, which is frequently known as *ledum camphor*. Since however it is not a ketone, but a tertiary alcohol, this name is confusing and should be replaced by *ledol*. *Ledol* was first isolated by Tropp¶ and it was more thoroughly investigated by Hjelt and Collan** and by Rizza.††

It was suggested by Semmler and Mayer,** on the basis of the molecular refraction ($[R_L]_D$ 67.35), that *ledol* was dicyclic and

* *Ber.* 1914, 47, 329.

† *Ibid.* 1912, 45, 1384.

‡ This hydrocarbon is not identical with the *dihydrocedrene* prepared by the catalytic hydrogenation of cedrene (p. 86) and it should therefore be designated *isodihydrocedrene*. The relationship of the two hydrocarbons has not been determined.

§ *Ber. Deut. pharm. Ges.* 1910, 20, 293.

|| *J.C.S.* 1930, p. 1908.

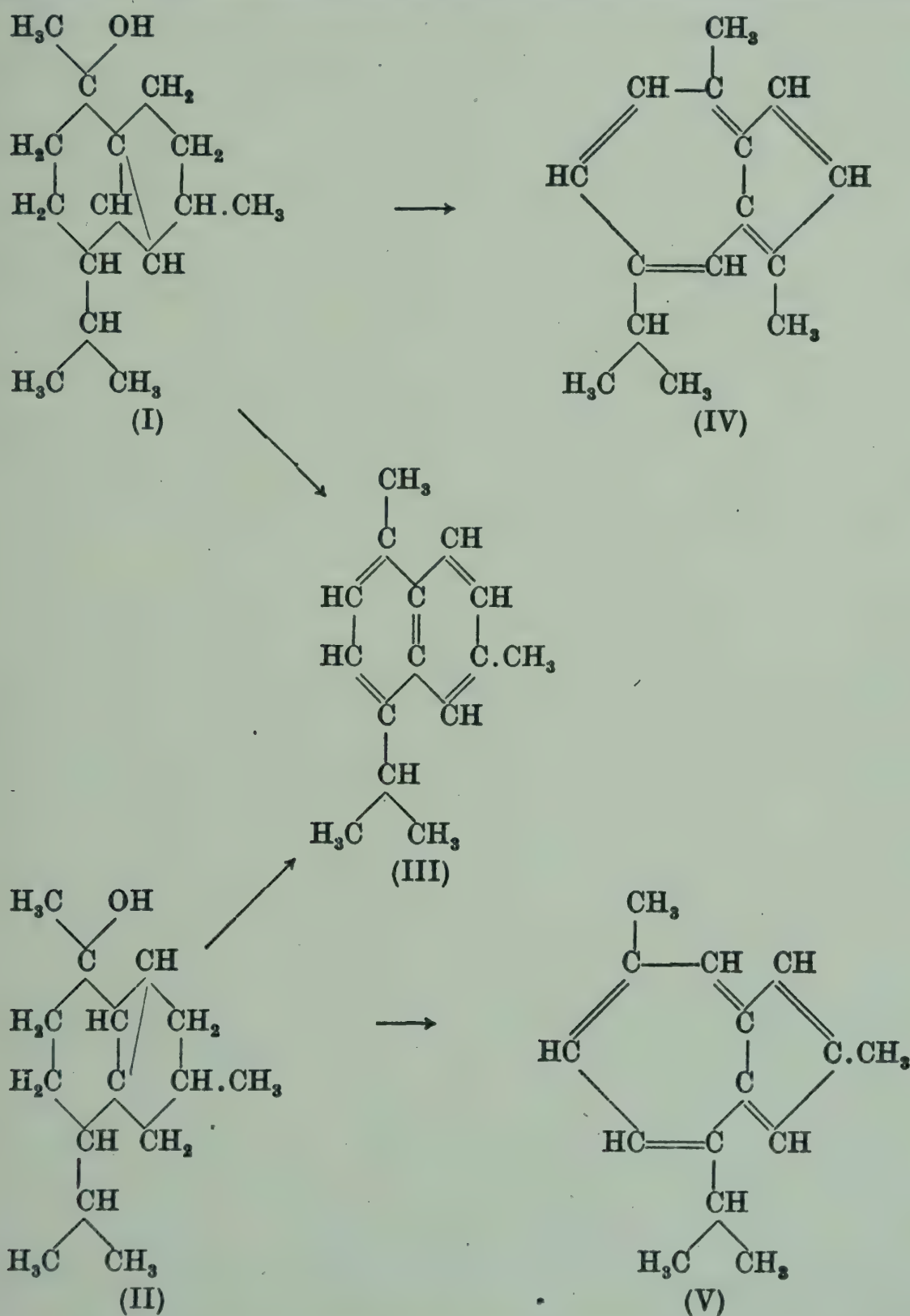
¶ *Ber.* 1875, 8, 542; compare Ivanov, *Jahresbericht*, 1876, 909.

** *Ber.* 1882, 15, 2500.

†† *J. Russ. Phys. Chem. Soc.* 1883, 15, 362; 1887, 19, 324; *Ber.* 1883, 16, 2311; 1887, 20, 562.

** *Ber.* 1912, 45, 1391.

contained one ethylenic linkage. The more recent investigations of Komppa and his collaborators* have shown this view to be untenable. Ledol is undoubtedly a saturated tertiary alcohol which readily loses water with the formation of the unsaturated hydrocarbon, *ledene* (see below). On heating with sulphur or selenium ledol yields cadalene and a mixture of azulenes. Komppa and Nyman suggest that ledol is most probably repre-

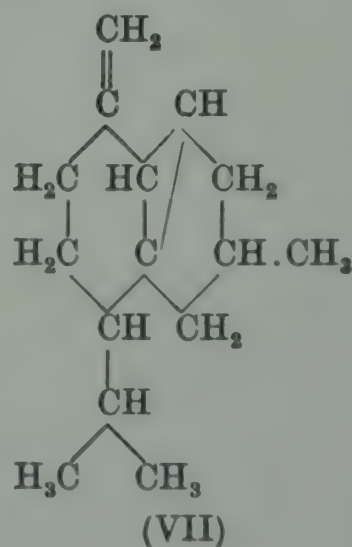
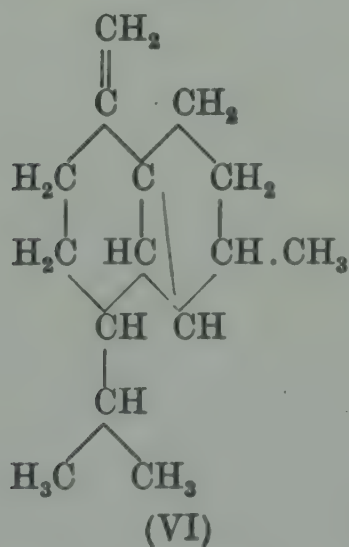


* *Z. angew. Chem.* 1932, **45**, 588; *Kong. Norsk. Vidensk. Skr.* 1933, **1**, 1; Komppa and Nyman, *Compt. rend. Trav. Lab. Carlsberg*, 1938, **22**, 272; Nyman and Mikander, *Suomen Kem.* 1941, **14** B, 3; cf. Kirialow, *J. Gen. Chem. U.S.S.R.* 1949, **19**, 2123.

sented by either (I) or (II), either of which would yield cadalene on dehydrogenation accompanied by fission of the *cyclopropane* ring. An analogy is suggested in the conversion of carane into *p*-cymene.* The formation of the azulenes involves a molecular rearrangement, when (I) and (II) might be expected to give (IV) and (V) respectively. It is of interest to note that Nyman and Mikander† found that the azulenes obtained by dehydrogenation with sulphur and selenium differed. With the former reagent the azulene was a dark blue oil, *s*-trinitrobenzene derivative, m.p. 152–152.5°, with the latter a violet oil, *s*-trinitrobenzene derivative, m.p. 146–147°. The melting-point of the trinitrobenzene adduct of the azulene formed with sulphur is in agreement with that recorded for the corresponding derivative of S-guaiazulene (IV) (m.p. 151.5°).‡ If this suggested identity be correct then ledol should be represented by (I).

Ledol crystallises in colourless needles, m.p. 104–105°, b.p. 290°/760 mm., d_{20}^{100} 0.9094, n_D^{40} 1.4667, $[\alpha]_D + 8.0^\circ$: It sublimes readily below its melting-point. It can be easily characterised by the preparation of its crystalline *chromate*, $(C_{15}H_{25})_2CrO_4$, m.p. 92°.§

Ledol loses water readily either by digestion with acetic anhydride or by the action of sulphuric acid|| to give the unsaturated hydrocarbon, *ledene*, b.p. 115–118°/6 mm. This is probably best prepared by heating the alcohol with potassium hydrogen sulphate.¶ It does not yield any crystalline derivatives.



* Zelinsky and Lewina, *Annalen*, 1929, **472**, 65.

† *Loc. cit.*

‡ Compare Pfau and Plattner, *Helv. Chim. Acta*, 1936, **19**, 858.

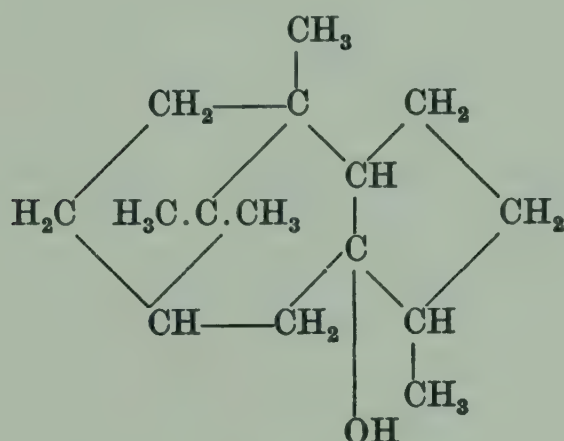
§ Wienhaus, *Ber.* 1914, **47**, 330.

|| Hjelt, *Ber.* 1895, **28**, 3088.

¶ Komppa, *loc. cit.*

On catalytic hydrogenation, the saturated hydrocarbon, *ledane*, b.p. 112–115°/8 mm., d_4^{20} 0.9075, n_D^{20} 1.4923, is formed. Ledene probably contains an *exocyclic* ethylenic linkage, since it gives formaldehyde on ozonolysis, and on the basis of (I) or (II) may be represented by (VI) or (VII). Ledol does not react with the halogens, whilst with hydrogen chloride ledene is formed. Hjelt prepared *ledyl chloride*, $C_{15}H_{25}Cl$, by treatment of the alcohol with phosphorus pentachloride; this chloride, when warmed with quinoline, yields ledene.

PATCHOULI ALCOHOL
(*PATCHOULI CAMPHOR*)



In 1869 Gal* observed that patchouli oil, which is obtained from the leaves of *Pogostemon Patchouly* var. *suavis*, deposited a crystalline substance, m.p. 54–55°, which he considered to have the composition, $C_{15}H_{28}O$, and to which he gave the name *patchouli camphor*. The later investigations of Montgolfier† showed, however, that it had the composition $C_{15}H_{26}O$.

It was suggested by Semmler and Mayer‡ that patchouli alcohol, m.p. 56°, b.p. 140°/8 mm., d_{29}^{65} 0.9924, n_D^{65} 1.5029, $[\alpha]_D - 97.4^\circ$, was a tertiary alcohol and this received support from the preparation of a crystalline *chromate*.§ These and other investigations|| provided no evidence of the structure of the alcohol, although it was observed it readily lost water with the

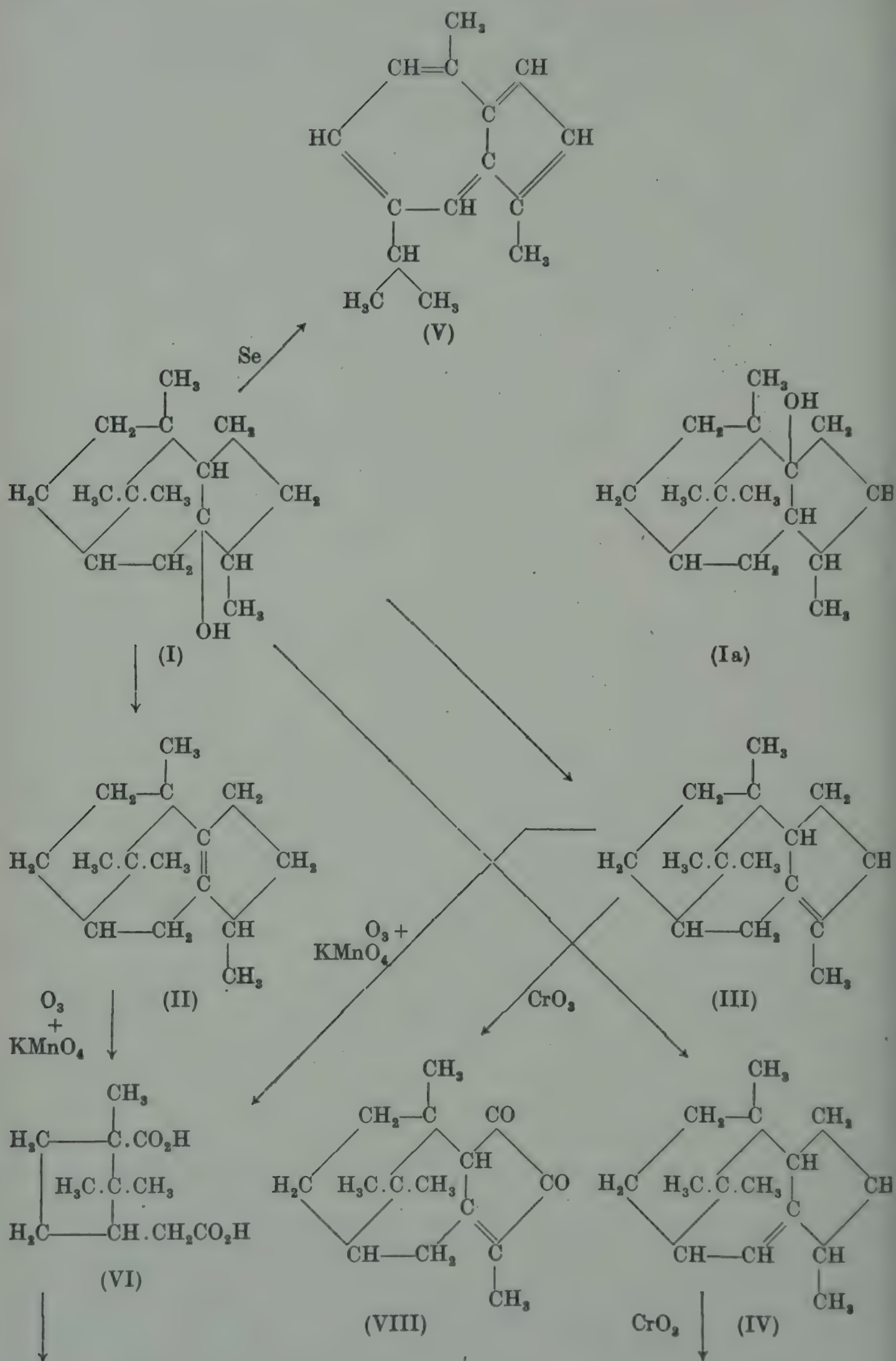
* *Compt. rend.* 1869, **63**, 406; *Annalen*, 1869, **150**, 374.

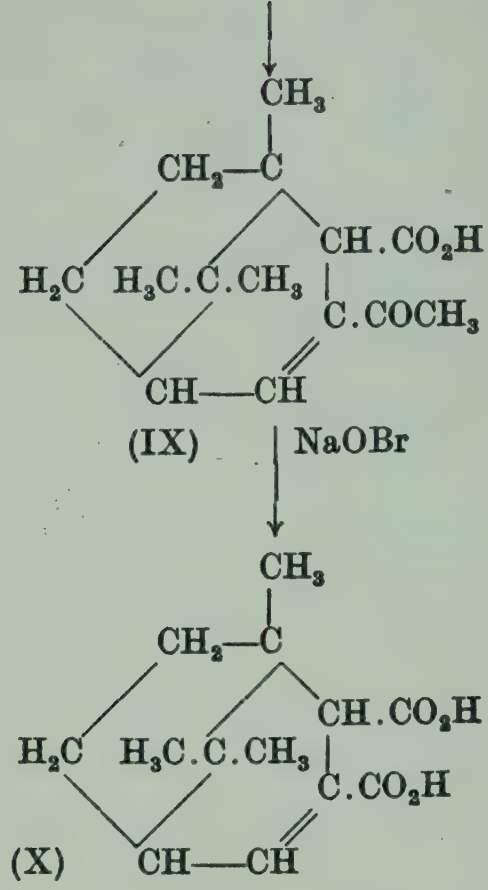
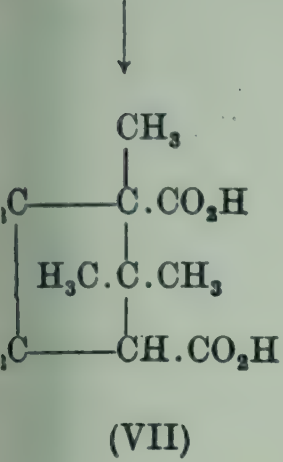
† *Compt. rend.* 1877, **84**, 88; *Bull. Soc. chim.* 1877 [ii], **28**, 414; *Ber.* 1877, **10**, 234.

‡ *Ber.* 1912, **45**, 1391.

§ Wienhaus, *Ber.* 1914, **47**, 322.

|| Wallach, *Annalen*, 1892, **271**, 299; 1894, **279**, 394; Gadamer and Amenomiya, *Arch. Pharm.* 1903, **241**, 22.





formation of a hydrocarbon, *patchoulene*, b.p. 112–115°/12 mm. This has been shown by Treibs* to be a mixture, its physical constants showing a marked variation depending upon the dehydrating agent employed.

Dehydrating agent	$d_4^{20^\circ}$	$n_D^{20^\circ}$	$\alpha_D^{20^\circ}$
Acetic anhydride	0.9506	1.5043	– 46.25°
Formic acid	0.9305	1.4981	– 37.0°
Hydrochloric acid	0.9259	1.4922	– 15.5°
Sulphuric acid	0.9211	1.4918	– 5.38°

As the outcome of an elegant investigation Treibs has provided evidence that patchouli alcohol is most probably represented by (I), patchoulene being a mixture of (II), (III) and (IV) in varying proportions. On dehydrogenation with sulphur or selenium the hydrocarbon gave only resinous products, but from the alcohol *S-guaiazulene* (V) was obtained. The alcohol was extremely resistant to the action of oxidising agents but ozonolysis of patchoulene gave in small yield a *ketone*, C₁₅H₂₂O, b.p. 125–130°/10 mm., $d_4^{20^\circ}$ 1.0143, and a *hydroxyketone*, C₁₅H₂₂O₂, b.p. 151–154°/10 mm., $d_4^{20^\circ}$ 1.0503, volatile in steam. The main product of the oxidation, which was not volatile in steam, gave on further oxidation with potassium permanganate *d-homocamphoric acid* (VI) and *d-camphoric acid* (VII). The formation

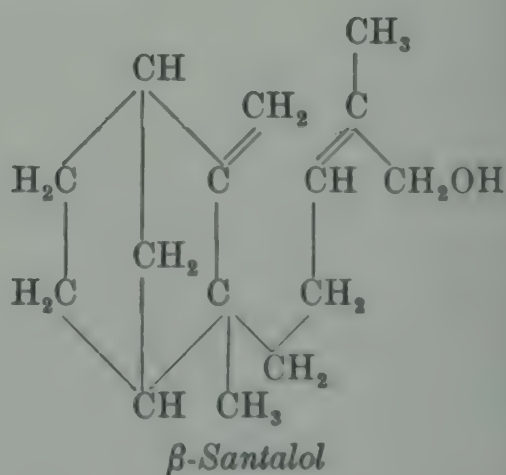
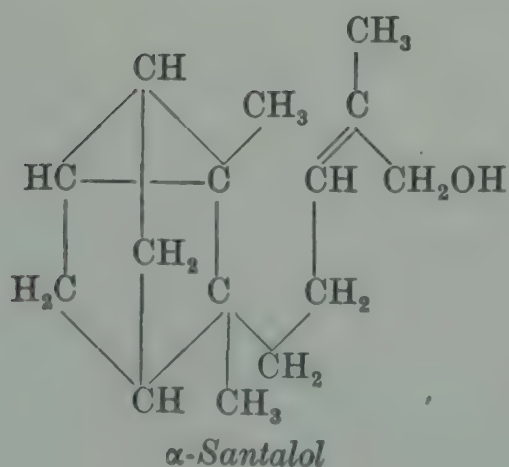
* *Annalen*, 1949, 564, 141.

of guaiazulene and of *d*-homocamphoric acid left little doubt that patchoulene must be represented by (II) or (III) and is most probably a mixture of the two substances. Evidence for the presence also of (IV) is referred to below. These experiments suggest further that the hydroxyl group in patchouli alcohol must be situated at the bridge as in (I) or (Ia) and confirmation of this was obtained by the oxidation of patchoulene with chromic acid. Dependent somewhat on the conditions employed the products consisted of (a) a liquid ketone, $C_{15}H_{22}O$, probably identical with that obtained on ozonolysis, from which no crystalline derivatives could be prepared and the structure of which was not determined, (b) a crystalline yellow 1:2-diketone, $C_{15}H_{22}O_2$, m.p. $91-91.5^\circ$, and (c) an unsaturated keto-carboxylic acid, $C_{14}H_{22}O_3$, m.p. 168° .

Treibs has suggested that the diketone, which was characterised by the preparation of a *dioxime*, m.p. $247-248^\circ$ and a *di-phenylsemicarbazone*, m.p. $252-253^\circ$, is best represented by (VIII) being derived from (III). The keto-carboxylic acid may be formulated as (IX) resulting from the oxidation of (IV). On further oxidation with sodium hypobromite in alkaline solution it gave a *dibasic acid*, $C_{13}H_{18}O_4$, (X), m.p. $131-132^\circ$, *anhydride*, m.p. $105-106^\circ$.

It may reasonably be deduced from these experiments that patchouli alcohol is best represented by (I). Only from an alcohol having this structure can the hydrocarbons (III) and (IV) be derived. (II), which can be formed from both (I) and (Ia), and (III) would yield homocamphoric acid but only (IV) can give a keto-acid containing an acetyl group.

THE SANTALOLS



The principal constituent of East Indian sandalwood oil is a mixture of alcohols which, in view of their use in pharmacy, have been very thoroughly investigated. Chapoteaut* was the first to examine the oil, and he isolated from the fraction, b.p. 300–310°, two substances, which he considered to have the composition $C_{15}H_{24}O$ and $C_{15}H_{26}O$. He suggested that the former, which was present in larger amount, was an aldehyde and the latter an alcohol. Parry,† who determined the acetyl value of the oil, concluded that 83–90 per cent. of alcohols were present, whilst Chapman and Burgess,‡ who oxidised the oil and obtained an acid, m.p. 76°, which they designated santalenic acid, inclined to the view of Chapoteaut, that the principal constituent was an aldehyde. The experiments of Dulière§ and Schimmel and Co.|| showed, however, that this was incorrect, the oil consisting mainly of an alcohol or mixture of alcohols, $C_{15}H_{24}O$, which reacted with phthalic anhydride in benzene solution to yield a hydrogen phthalate. The “santalol”, obtained by the hydrolysis of the hydrogen phthalate, could be separated by distillation into fractions having different rotatory powers, but the two alcohols present were not obtained pure.

The greater part of our knowledge of the santalols is due to the investigations of Semmler and his collaborators (for references to the literature see p. 98). They did not succeed in separating the two alcohols completely by fractional distillation, nor were the alcohols obtained in a state of purity by Paolini and Divizia¶ by fractional crystallisation of the strychnine salts of their hydrogen phthalates. The purest specimens of the α - and β -santalols have only been prepared by a combination of these two processes.** For α -santalol the constants b.p. 166–167°/14 mm., $d_{25}^{25} 0.9770$, $n_D^{25} 1.5017$, $\alpha_{5461} + 10.3^\circ$, $\alpha_{5780} + 9.0^\circ$ have been recorded and for β -santalol, b.p. 177–177.5°/17 mm., $d_{25}^{25} 0.9717$, $n_D^{25} 1.5100$, $\alpha_{5461} - 87.1^\circ$, $\alpha_{5780} - 76.1^\circ$.

Both α - and β -santalol must be primary alcohols, since they react readily with phthalic anhydride in benzene solution.

* *Bull. Soc. chim.* 1882 [ii], 37, 303.

† *Pharm. J.* 1895, 55, 118.

‡ *Proc. C.S.* 1896, 12, 140.

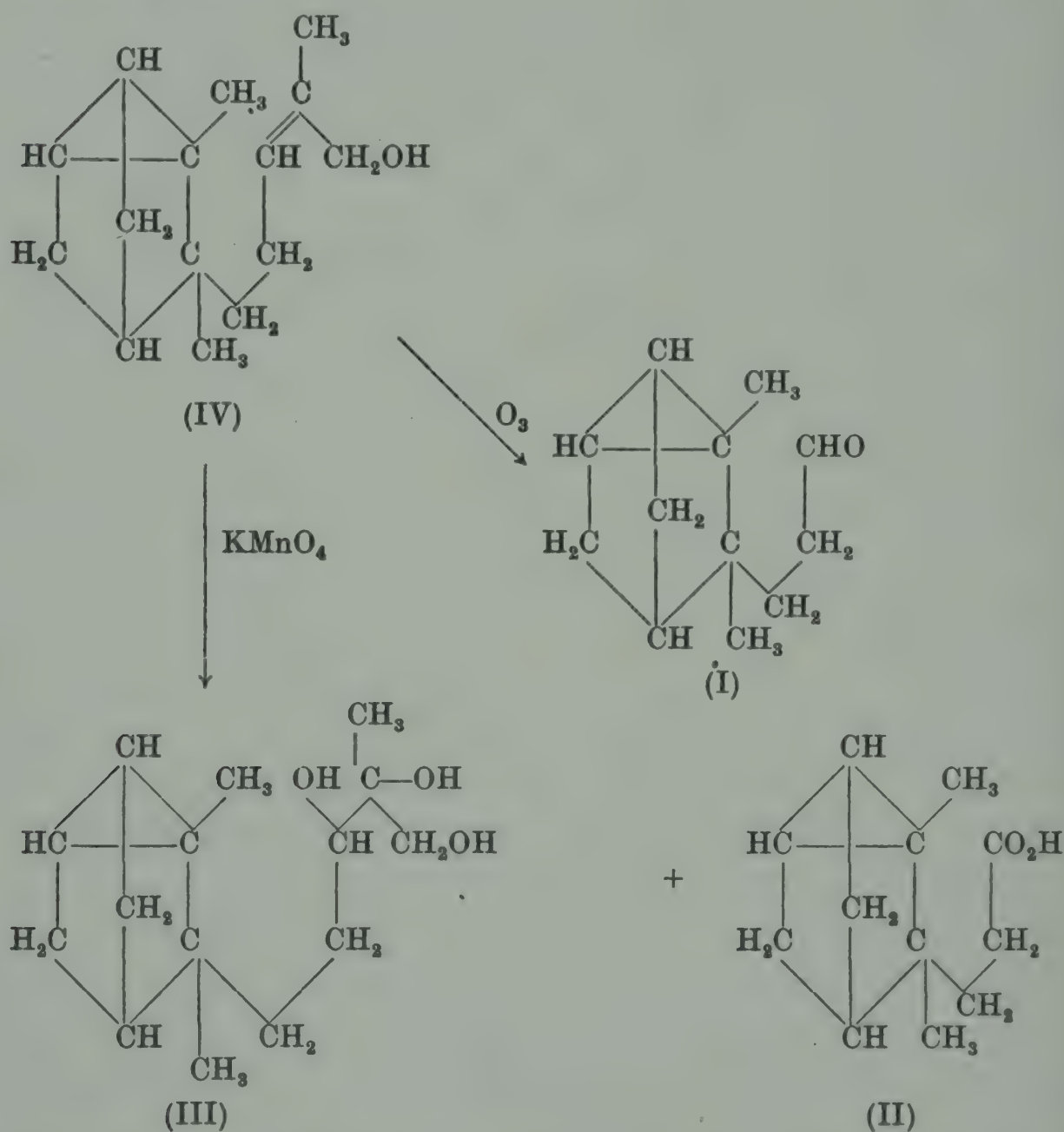
§ *J. Pharm. Chim.* 1898 [vi], 7, 553.

|| *Schimmel's Report*, 1899, I, 43.

¶ *Atti R. Accad. Lincei*, 1914 [v], 23, II, 226.

** Bradfield, Penfold and Simonsen, *J.C.S.* 1935, 309; Guha and Bhattacharyya, *J. Ind. C.S.* 1944, 21, 261.

α -Santalol gave on ozonolysis *tricycloekasantalal* (I), b.p. 109–110°/10 mm., d^{20}_D 0.9845, n_D 1.4852, $\alpha_D + 13.3^\circ$, *semicarbazone*, m.p. 156°,* and *tricycloekasantalic acid* (II).† If potassium permanganate was used as the oxidising agent, then in addition to this acid, a glycol, *dihydroxydihydro- α -santalol* (III), b.p. 215–220°/10 mm., was obtained. α -Santalol must be represented therefore by (IV).



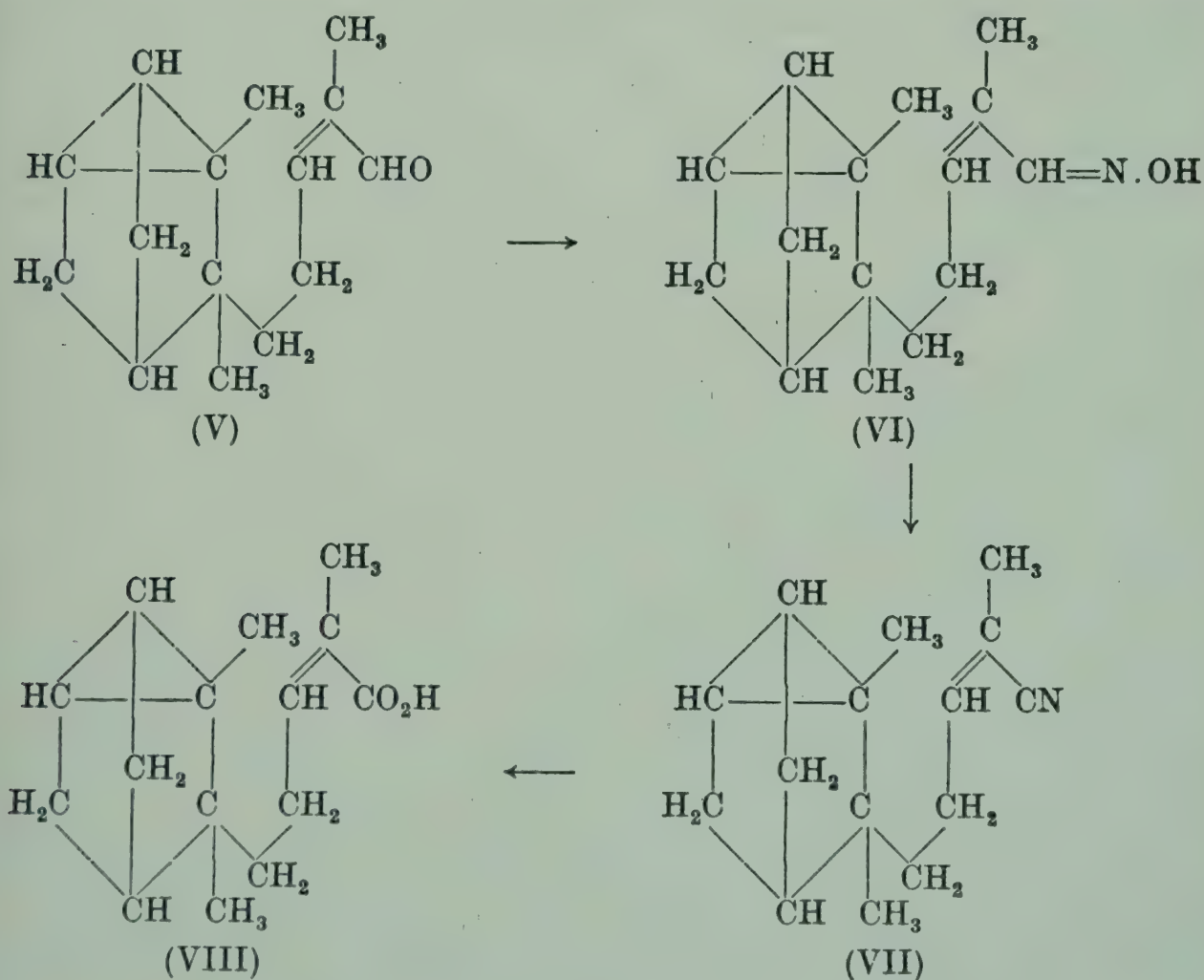
α -Santalol can be characterised by the preparation of the *strychnine* salt of the *hydrogen phthalate*, m.p. 144–145°, $[\alpha]_{5461} - 5.62^\circ$ (in benzene) and by the formation of the *allophanate*, m.p. 162–163°.

* For proof of the structure of (I) see p. 100.

† The acid, *santalenic acid*, m.p. 76°, prepared by Chapman (*J.C.S.* 1901, 79, 134) by the oxidation of sandalwood oil, was probably *tricycloekasantalic acid*. He considered it had the composition $C_{13}H_{20}O_2$.

On catalytic hydrogenation in the presence of platinum black Semmler and Risse* obtained a hydrocarbon, *tetrahydro- α -santalene*, $C_{15}H_{28}$, b.p. $115-116^{\circ}/9$ mm., $d^{20^{\circ}} 0.8655$, $n_D 1.4691$, $[\alpha]_D + 5.36^{\circ}$, replacement of the hydroxyl group with hydrogen having occurred, together with reduction of the ethylenic linkage and fission of one of the rings. This hydrocarbon is possibly identical with the tetrahydrosantalene mentioned on p. 101 and which is obtained from α -santalene by an indirect method. When α -santalol was reduced with hydriodic acid and red phosphorus a hydrocarbon, $C_{15}H_{26}$, b.p. $125-130^{\circ}/12$ mm., $d^{20^{\circ}} 0.8999$, $n_D 1.4871$, was obtained which was probably not homogeneous.

α -Santalol is oxidised by chromic acid to α -santalaldehyde (α -santalal), $C_{15}H_{22}O$, b.p. $152-155^{\circ}/10$ mm., $d^{20^{\circ}} 0.995$, $n_D 1.5107$, $\alpha_D + 13^{\circ}$, *semicarbazone*, m.p. 230° , which must be represented by (V).† The *oxime* (VI), m.p. $104-105^{\circ}$, of α -santalal, gave on digestion with acetic anhydride and sodium acetate the *nitrile* (VII), b.p. $162-166^{\circ}/9$ mm., which could be hydrolysed to the acid, α -santalallic acid (VIII), $C_{15}H_{22}O_2$, b.p. $192-195^{\circ}/9$ mm. (see



* Ber. 1913, 46, 2306.

† Semmler and Bode, *ibid.* 1907, 40, 1126.

p. 107). The partial synthesis of α -santalal has been reported recently by Guha and Bhattacharyya.* It can be reconverted into α -santalol by reduction by the aluminium isopropoxide method.

By the action of thionyl chloride on α -santalol in pyridine solution α -santaly chloride, b.p. 155–158°/14 mm., $n_D^{20.5}$ 1.5042, $\alpha_{5461} + 7.6^\circ$, can be prepared.† According to Semmler and Bode,‡ this chloride is obtained also by the action of phosphorus pentachloride on the alcohol, but, since they used an impure alcohol in their experiments, their chloride cannot have been homogeneous. Condensation of α -santaly chloride with ethyl sodiomalonate afforded *ethyl α -santaly malonate*, b.p. 212–213°/13 mm., yielding on hydrolysis *α -santaly malonic acid*, m.p. 120–121°, $[\alpha]_{5461} + 4.7^\circ$ (in methyl alcohol), which gave on decarboxylation *α -santaly acetic acid*, b.p. 188°/2 mm. *Dihydro- α -santaly acetic acid*, b.p. 208–210°/15 mm., was prepared similarly by decarboxylation of crude *dihydro- α -santaly malonic acid* obtained by catalytic reduction of α -santaly malonic acid with palladised charcoal in alcoholic solution. On the basis of (IV) α -santaly chloride should be represented by (IX), α -santaly malonic and acetic acids by (X) and (XI) respectively and dihydro- α -santaly acetic acid by (XII).

Brief reference has already been made (Vol. I, p. 3) to the anomalous results obtained on the oxidative degradation of α -santaly malonic acid. On ozonolysis the acid gave *tricycloekasantalic acid* (XIII); whilst with potassium permanganate in alkaline solution *3-keto- δ -teresantaly butyl malonic acid* (XIV), *semicarbazone*, m.p. 172–173°, was obtained. This latter acid can result only from an acid represented by (Xa).

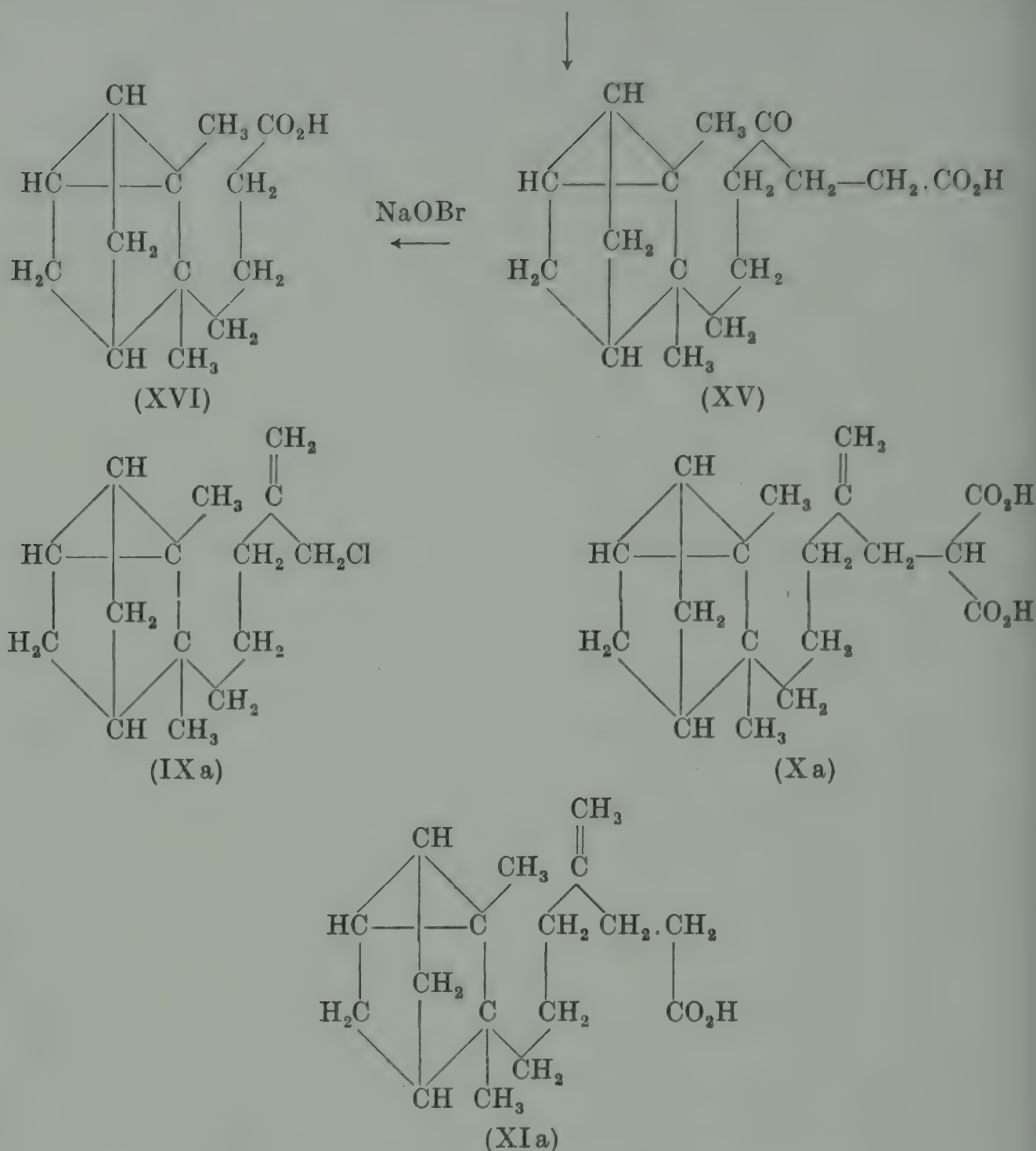
Similar results were recorded also for the oxidation of α -santaly chloride; with potassium permanganate *tricycloekasantalic acid* (XIII) resulted, but on ozonolysis an appreciable quantity of formaldehyde was obtained, indicating the presence of the chloride (IXa).

α -Santaly acetic acid gave on degradation with potassium permanganate a liquid *keto-acid*, $C_{16}H_{24}O_3$. *methyl ester*, b.p. 211°/17 mm., the *semicarbazone* of which had m.p. 176–177° and

* *J. Ind. C.S.* 1944, **21**, 280.

† Bradfield, Penfold and Simonsen, *loc. cit.*

‡ *Ber.* 1907, **40**, 1126.



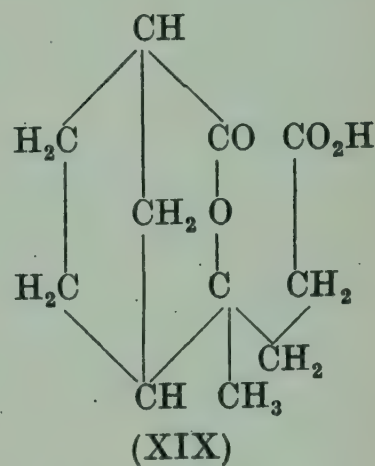
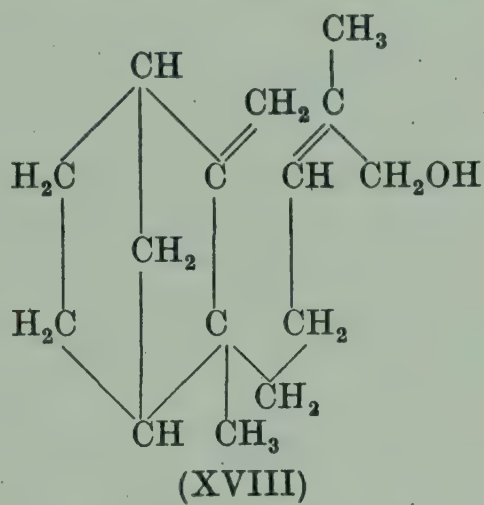
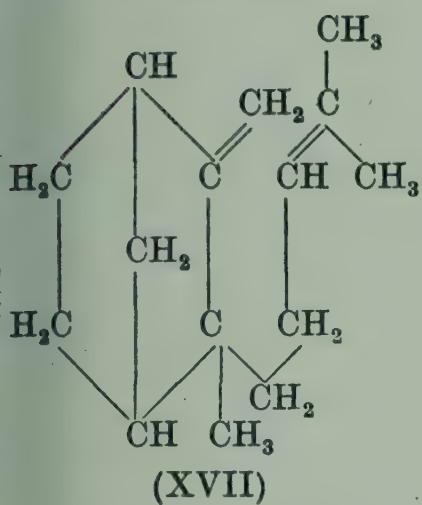
the *phenylsemicarbazone* m.p. 192–193°. This keto acid must have been (XV), since it gave on further oxidation with sodium hypobromite 3-*teresantalylpropionic acid* (XVI), *methyl ester*, b.p. 140–145°/15 mm. Again this experiment indicates a modified formula (XIa) for α -santalylacetic acid.

These experiments afford an interesting example of the *isopropenyl-isopropylidene* type change to which attention has been previously directed. For convenience α -santalyl chloride will in the sequel be assumed to be represented by (IX) and its derivatives by the corresponding formulae.

Since α -santalol is a primary alcohol, it combines readily with acids, and a large number of santalyl esters have been prepared,

some of which have found use in medicine. They are almost without exception mixtures of the esters of the α - and β -santalols.

It had been assumed by the earlier workers, without direct experimental proof, that β -santalol and β -santalene were related in the same way as α -santalol and α -santalene. Since β -santalene has now been assigned the formula (XVII), this assumption would imply that β -santalol should be represented by (XVIII). This view has received support from the observation of Ruzicka and



Thomann* that the *lactonic acid* (XIX), b.p. $134^{\circ}/0.1$ mm., $d_4^{22^{\circ}}$ 1.1424, $n_D^{22^{\circ}}$ 1.4827, could be isolated from amongst the products formed by the ozonolysis of β -santalol. As has been previously mentioned (p. 103), this lactonic acid was obtained also by the ozonolysis of β -santalene. Ruzicka and Thomann have suggested that it is probable that the alcohols used in their experiments were not quite pure, since their α -santalol also gave this lactonic acid on ozonolysis in about half the yield, but this cannot be regarded as invalidating their conclusions. Recently Bhattacharyya has described the direct conversion of α -santalol to β -santalol, thus confirming these views on the nature of the latter alcohol.[†]

Experiments on the constitution of β -santalol have been carried out also by Bradfield, Penfold and Simonsen.[‡] They showed that on ozonolysis both α - and β -santalols gave formaldehyde and acetone resulting from the side chain tautomerism referred to above. They were, however, able to prove the close structural relationship of the two alcohols by the experiments summarised below.

* *Helv. Chim. Acta*, 1935, 18, 355.

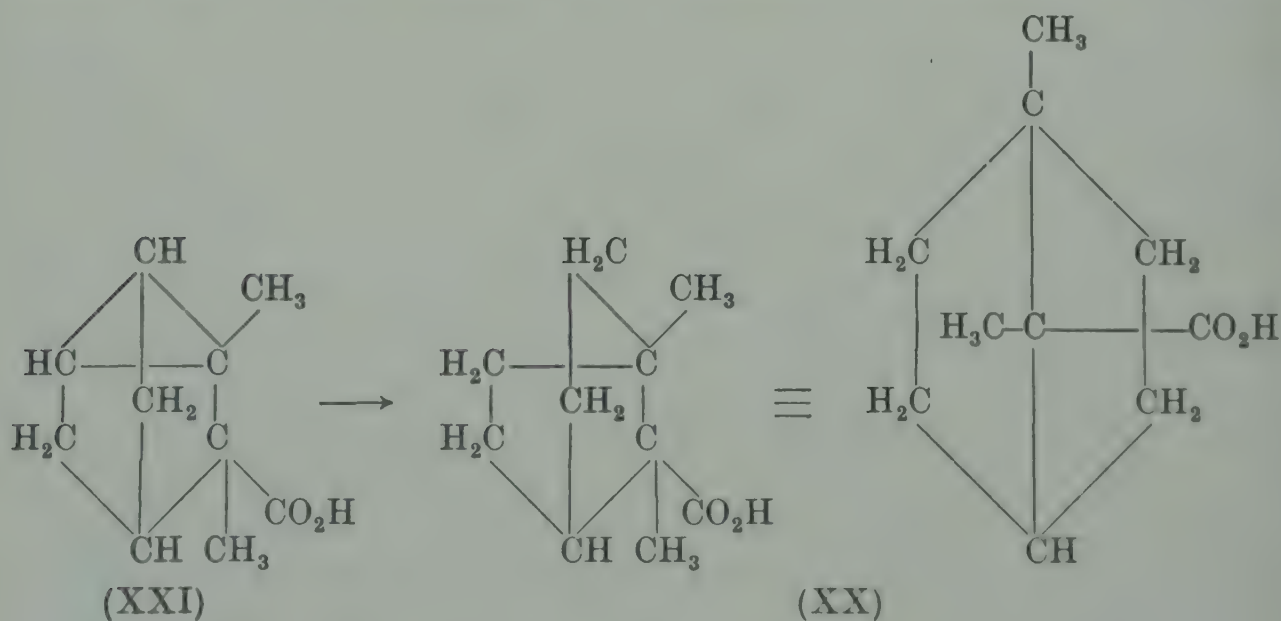
† *Science and Culture*, 1947, 13, 206, 207.

‡ *J.C.S.* 1935, 309.

From β -santalyl chloride, b.p. $161^{\circ}/20$ mm., $n_D^{16^{\circ}}$ 1.5126, $\alpha_{5461} - 66.6^{\circ}$, β -santalylmalonic acid, m.p. $99-101^{\circ}$, $[\alpha]_{5461} - 60.0^{\circ}$ (in methyl alcohol) was prepared and from this, by catalytic hydrogenation followed by decarboxylation, tetrahydrosantalylacetic acid b.p. $210-213^{\circ}/16$ mm., p-bromophenacyl ester, m.p. $52-53^{\circ}$, diphenacyl ester, m.p. $61-62^{\circ}$, was obtained. This acid also resulted when dihydro- α -santalylacetic acid (p. 182) was treated with hydrogen bromide and the resulting bromo-acid reduced with sodium and alcohol.

Now it has been shown by Hasselström* that dihydroteresantalic acid (XX), prepared from teresantalic acid (XXI) by a very similar method of ring fission, is identical with π -apocamphan-carboxylic acid (Vol. II, p. 267). It would be anticipated therefore that the conversion of dihydro- α -santalylacetic acid (XII) to tetrahydrosantalylacetic acid (XXII) must proceed by a similar route as indicated in the diagram. On the other hand the reduction and decarboxylation of a β -santalylmalonic acid (XXIII), prepared from a β -santalol of the formula (XVIII), would be expected to lead to a tetrahydrosantalylacetic acid of the formula (XXIV). In spite of this discrepancy the formula (XVIII) for β -santalol has been further confirmed by a partial synthesis.†

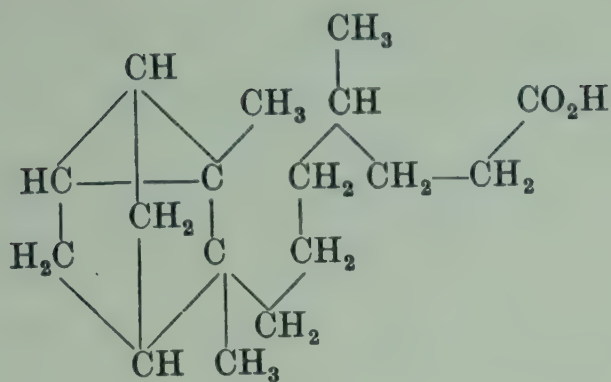
On catalytic hydrogenation in the presence of platinum black, β -santalol is stated‡ to give a mixture of tetrahydro- β -santalene, $C_{15}H_{28}$, b.p. $119^{\circ}/10$ mm., $d^{20^{\circ}}$ 0.8550, n_D 1.4661, $[\alpha]_D + 2.48^{\circ}$.



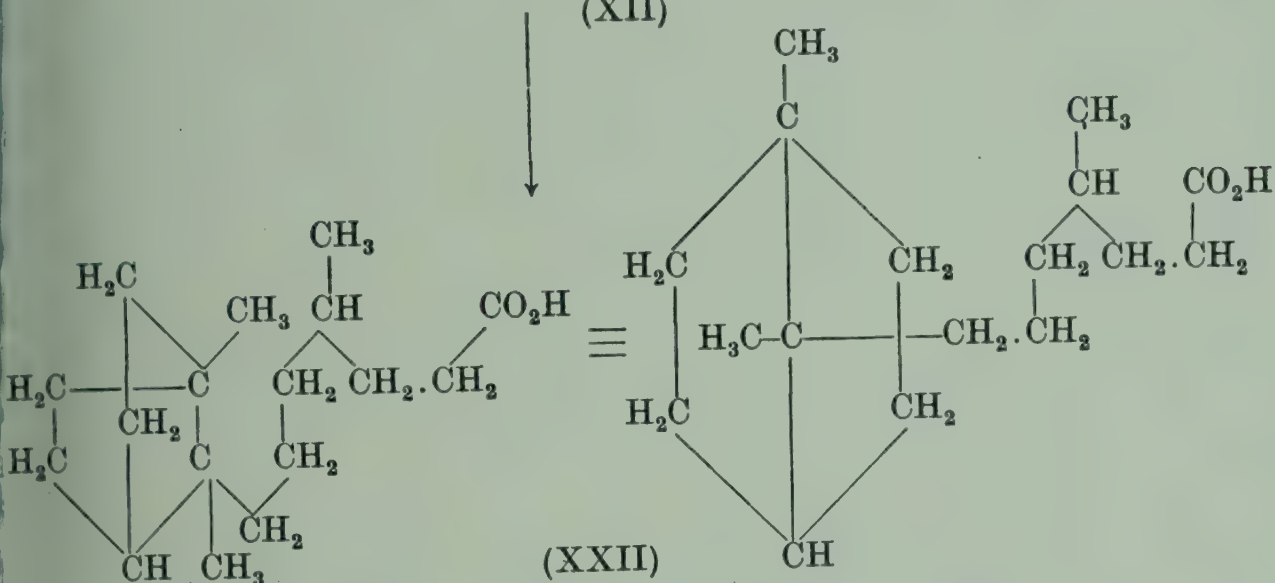
* J. Amer. C.S. 1931, 53, 1097.

† Bhattacharyya, Science and Culture, 1947, 13, 209.

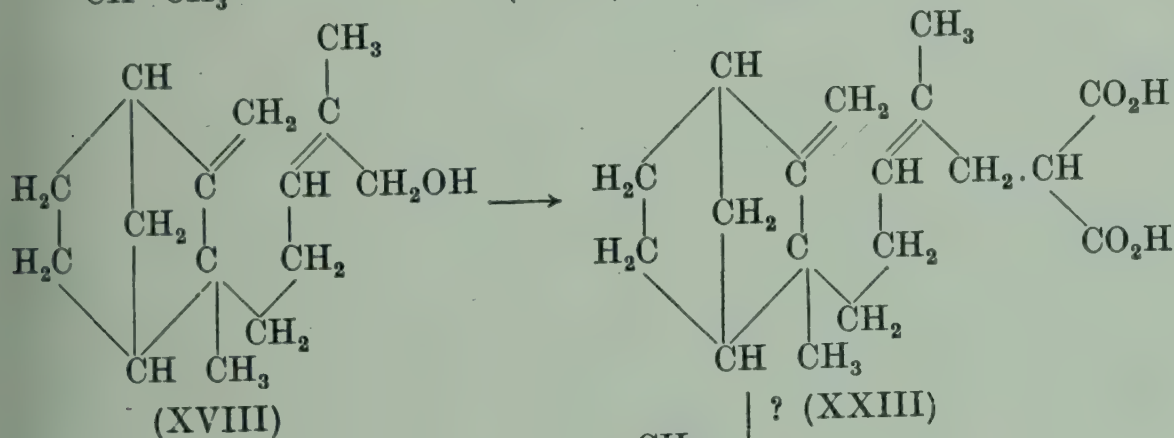
‡ Semmler and Risse, Ber. 1913, 46, 2306.



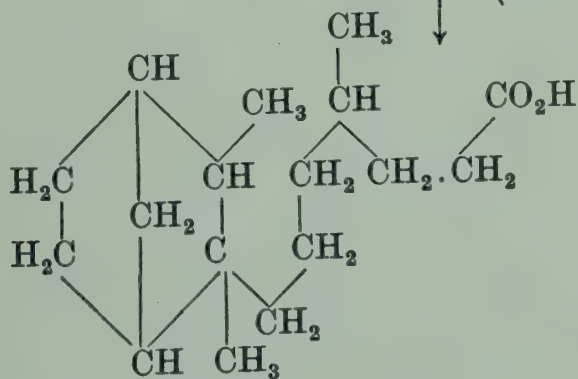
(XII)



(XXII)



(XVIII)

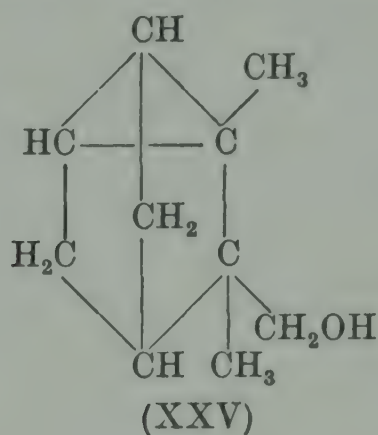


(XXIV)

and a saturated alcohol, *tetrahydro-β-santalol*, $C_{15}H_{28}O$, b.p. 155–160°/10 mm., d^{20}_D 0.9380, n_D 1.4847, $[\alpha]_D + 4.24^\circ$. Tetrahydro-β-santalene may be identical with tetrahydro-α-santalene, as their physical constants are in fair agreement, in spite of the opinion of Semmler and Bode to the contrary.

β -Santalol can be characterised by the preparation of the *strychnine salt* of the *hydrogen phthalate*, m.p. 134–135°, $[\alpha]_{5461} - 37.5^\circ$ (in benzene) and by the *allophanate*, m.p. 159–160°.

In addition to the two sesquiterpene alcohols, α - and β -santalols, Schimmel and Co.* have shown the alcohol *teresantalol* (XXV), $C_{10}H_{16}O$, m.p. 112–114°, b.p. 95–98°/9 mm., $[\alpha]_D + 11.58^\circ$, to be present in sandalwood oil (see Vol. II, p. 264).



E. ALCOHOLS OF UNKNOWN CONSTITUTION

THE BETULENOLS

The mixture of dicyclic sesquiterpene alcohols formerly called *betulol*, but now termed the *betulenols*, was first found by Soden and Elze† to occur in the essential oil distilled from the leaf buds of *Betula alba* L., and was later investigated by Semmler, Jonas and Richter.‡ The inhomogeneity of the oil was demonstrated by Treibs,§ who was able to isolate three alcohols for which he suggested the names α -, β - and γ -betulenols. The α - and β -betulenols are primary alcohols readily forming hydrogen phthalates, while γ -betulenol is a tertiary alcohol. Since α -betulenol occurs as the acetate, treatment of the oil with phthalic anhydride readily separated β -betulenol, b.p. 155–157°/20 mm., $d^{15^\circ} 0.975$, $n_D 1.5132$, $\alpha_D - 36^\circ$, as the hydrogen phthalate. By hydrolysis of the residual oil and further treatment with phthalic anhydride α -betulenol, b.p. 154–156°/20 mm., $d^{15^\circ} 0.978$, $n_D 1.5148$, $\alpha_D - 19.5^\circ$, was separated from γ -betulenol, b.p. 157–158°/20 mm.,

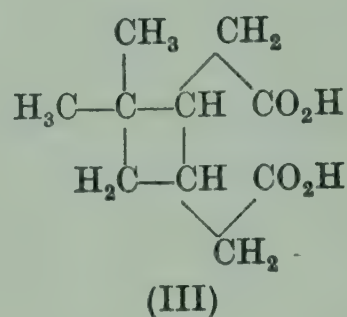
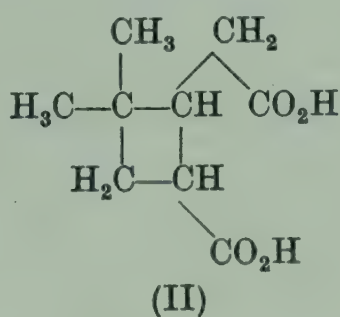
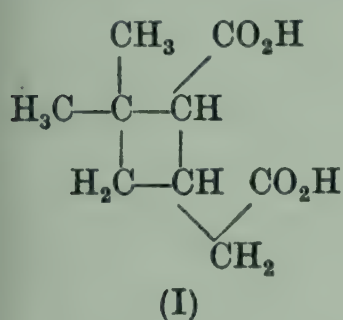
* *Schimmel's Report*, 1910, Oct., p. 121.

† *Ber.* 1905, 38, 1636.

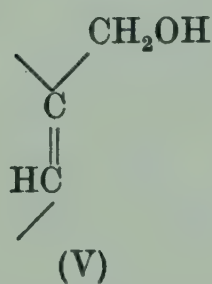
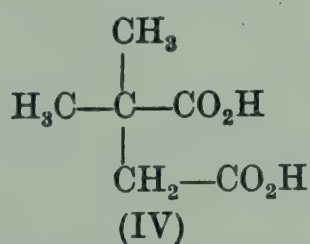
§ *Ber.* 1936, 69, 41; *ibid.* 1938, 71, 612.

‡ *Ibid.* 1918, 51, 420.

d_{15}° 0.969, n_D 1.5102, α_D -19.5° . All three alcohols gave, on oxidation with potassium permanganate followed by hot dilute nitric acid, *betulenolic acid, dimethyl ester*, b.p. $140-150^{\circ}/20$ mm., d_{15}° 1.041 to 1.050, n_D 1.4506 to 1.4540, α_D $+44.4^{\circ}$ to $+49.0^{\circ}$. This acid must have been a mixture of *caryophyllenic acid* (I) or (II),* and *homocaryophyllenic acid*, probably (III) (see p. 48 *et seq.*), since, from the dimethyl ester, two *anilides* were prepared, m.p.s 280° and 179° respectively, identical with the anilides of the acids derived from the caryophyllenes. In agreement with this view betulenolic acid could be further degraded by nitric acid to *as-dimethylsuccinic acid* (IV).



The close relationship between the betulenols and the caryophyllenes implied by these experiments was confirmed by Treibs,[†] who oxidised caryophyllene with selenium dioxide and isolated a primary *alcohol* from the reaction product, b.p. $157-159^{\circ}/20$ mm., d_{15}° 0.880, n_D^{15} 1.5173, $[\alpha]_D^{15}$ -14.5 , with properties very similar to those of α -betulenol. It is likely therefore that at least α -betulenol possesses the partial formula (V), derived from the appropriate portion of the caryophyllene molecule (compare p. 39 *et seq.*).



In addition to the betulenols, birch bud oil contains a bicyclic, triply unsaturated sesquiterpene, $\text{C}_{15}\text{H}_{24}$, b.p. $132-135^{\circ}/20$ mm., d_{15}° 0.911, n_D 1.502, α_D -11.5° , which should be known as *betulenene*. This hydrocarbon is closely related to the betulenols, for it furnished a mixture of caryophyllenic and homocaryophyllenic acids on oxidation in exactly the same way as did the

* See footnote p. 50.

† *Ber.* 1938, 71, 1794.

betulenols themselves (see above). Betulenene is not identical with the mixture of hydrocarbons called *betulene*, which were obtained by Semmler, Jonas and Richter,* when betulenol was converted, by the action of phosphorus pentachloride, to *betulenyl chloride* and this chloride reduced with sodium and alcohol.

BULNESOL

The bicyclic, tertiary sesquiterpene alcohol, *bulnesol*, $C_{15}H_{26}O$, m.p. 69–70°, b.p. 136–138°/4 mm., $d_4^{70^\circ}$ 0.9389, $n_D^{70^\circ}$ 1.4892, occurs in association with guaicol (see p. 156) in guaicum wood oil.† Bulnesol contains one ethylenic linkage, for on catalytic hydrogenation the saturated *dihydrobulnesol*, $C_{15}H_{26}O$, m.p. 75–76°, was prepared. On digestion of bulnesol with formic acid the corresponding doubly unsaturated hydrocarbon, *bulnesene*, $C_{15}H_{24}$, b.p. 113.5–115°/6 mm., d^{20° 0.9149, $n_D^{20^\circ}$ 1.5047, α_D –14.4°, which was probably a mixture of isomers, was obtained. By catalytic hydrogenation bulnesene was converted to the corresponding saturated hydrocarbon, *bulnesane*, $C_{15}H_{28}$, b.p. 107–109°/5 mm., d^{20° 0.8910, $n_D^{20^\circ}$ 1.4799, α_D –12.7°.

CALAMENOL

The alcohol, *calamenol*, $C_{15}H_{24}O$, occurs in the fraction of the oil derived from the rhizomes of *Acorus Calamus* L. which boils at 150–160°/13 mm., d^{20° 0.9611, n_D 1.5098, but it is doubtful if the alcohol has been obtained pure and quite free from asarone, which is a constituent of the natural oil. The alcohol was probably first isolated by Thoms and Beckström,‡ and it has been investigated more recently by Semmler and Spornitz§ and by Ruzicka, Meyer and Mingazzini.||

Calamenol does not yield any crystalline derivatives and it is somewhat unstable, readily losing water with the formation of the hydrocarbon, *calamenene*, $C_{15}H_{22}$, b.p. 136–143°/15 mm., $d_{19}^{20^\circ}$ 0.9324, n_D 1.5317, $[\alpha]_D$ +6°. This hydrocarbon, which contains three ethylenic linkages, can be hydrogenated in the

* *Loc. cit.*

† *Schimmel's Report*, 1929, p. 267.

‡ *Ber.* 1901, **34**, 1021; 1902, **35**, 3187, 3195.

§ *Ibid.* 1913, **46**, 3704.

|| *Helv. Chim. Acta*, 1922, **5**, 358.

presence of platinum black to a saturated terpene, $C_{15}H_{28}$, identical probably with that obtained by the hydrogenation of calamene (p. 107). On dehydrogenation with sulphur, calamenol yields cadalene.

It is probable that calamenene is identical with the hydrocarbon obtained by dehydration of calamendiol (see p. 142), and, accordingly, the two alcohols must be closely related in structure.*

COSTOL

The sesquiterpene alcohol, *costol*, $C_{15}H_{24}O$, was separated by Semmler and Feldstein[†] from oil of costus, which is obtained from the roots of *Saussurea Lappa*. It is a primary alcohol and, when purified through its hydrogen phthalate, it boils at 169–171°/11 mm., d^{21° 0.9803, n_D 1.5200, $[\alpha]_D + 13^\circ$. It may be deduced from its physical constants that costol is a dicyclic alcohol and contains two ethylenic linkages. On oxidation with chromic acid it yields an *aldehyde*, $C_{15}H_{22}O$, b.p. 164–165°/15 mm., d^{22° 0.9541, n_D 1.5064, $[\alpha]_D + 24^\circ$, *semicarbazone*, m.p. 217–218°. This aldehyde is not dicyclic and its formation is probably accompanied by ring closure. The actual nature of the relationship between the alcohol and the aldehyde has not, however, been determined.

On treatment with phosphorus pentachloride, costol yields *costyl chloride*, $C_{15}H_{23}Cl$, b.p. 160–165°/13 mm., d^{22° 1.005, n_D 1.5205, $[\alpha]_D + 32^\circ$, from which, by the action of sodium in alcoholic solution, a sesquiterpene, *isocostene*, $C_{15}H_{24}$, b.p. 130–135°/12 mm., d^{21° 0.9062, n_D 1.5024, $[\alpha]_D + 31^\circ$, can be prepared. This sesquiterpene, like the alcohol, is dicyclic and contains two ethylenic linkages, but there is no evidence that it is homogeneous.

CRYPTOMERADOL

The sesquiterpene tertiary alcohol, *cryptomeradol*, $C_{15}H_{26}O$, has been isolated from Japanese cedarwood oil (from *Cryptomeria japonica* Don.).[‡] It has m.p. 79–80°, b.p. 141–142°/4 mm.,

* Treibs, *Chem. Ber.* 1949, **82**, 530.

† *Ber.* 1914, **47**, 2687.

‡ *Schimmel's Report*, 1929, p. 267, compare Mizoshita, *Mem. Coll. Sci. Kyoto*, 1931, A, **14**, 273.

d^{60° 0.9515, $n_D^{60^\circ}$ 1.4932, $\alpha_D + 24.2^\circ$, *methyl ether*, b.p. 133.5–134.5°/5 mm., d^{20° 0.9503, $n_D^{20^\circ}$ 1.4960, $\alpha_D + 34.1^\circ$, and is probably bicyclic with one ethylenic linkage, since on catalytic hydrogenation it gives the saturated alcohol *dihydrocryptomeradol*, $C_{15}H_{28}O$, m.p. 81–82°, *methyl ether*, b.p. 124.5–125.5°/5 mm., d^{20° 0.9365, $n_D^{20^\circ}$ 1.4863, $\alpha_D + 11.3^\circ$. Cryptomeradol may be identical with the sesquiterpene alcohol, *sagittol*, $C_{15}H_{26}O$, isolated by Yanovsky* from the roots of *Balsamorhiza sagitta* (Pursh) Nutt.

CUBE BOL

A sesquiterpene alcohol, *cubebol*, $C_{15}H_{26}O$, was isolated by Henderson and Robertson† from oil of cubebs. Cubebol, m.p. 61–62°, can be characterised by the preparation of the *phenylurethane*, m.p. 186°, $[\alpha]_{5461} + 58.9^\circ$, the *dibromide* of which melts at 76–80°, and the α -*naphthylurethane*, m.p. 197–198.5°. It does not give cadinene dihydrochloride when treated with hydrogen chloride, and nothing is known regarding its constitution.

Cubebol does not appear to be identical with the so-called *cubebcamphor*, m.p. 68.7–70°, which was isolated by Blanchet and Sell‡ from oil of cubebs. According to Schmidt,§ this alcohol is not present in fresh oil of cubebs and it is possibly, therefore, an auto-oxidation product. It appears to lose water very readily, but it has not been investigated in recent years.

THE FUSANOLS

In 1922 Sudborough and Rao|| described the isolation from the oil derived from the wood of *Eucarya spicata* Sprague and Summerhayes of two alcohols, $C_{15}H_{24}O$, α - and β -*fusanols*. These alcohols, which were isolated through their hydrogen phthalates, were separated by fractional distillation, when α -fusanol had b.p. 146–149°/5 mm., d^{15° 0.9775, $n_D^{25^\circ}$ 1.5060, $[\alpha]_D^{25^\circ} + 5.7^\circ$, and β -fusanol b.p. 153–155°/5 mm., $d_{15}^{15^\circ}$ 0.9753, $n_D^{25^\circ}$ 1.5100, $[\alpha]_D + 2.6^\circ$. Although the difference in the rotatory powers of the

* *J. Amer. C.S.* 1930, **52**, 3446.

† *J.C.S.* 1926, p. 2811.

‡ *Annalen*, 1833, **6**, 294; compare Winkler, *ibid.* **8**, 203.

§ *Arch. Pharm.* 1870, **191**, 23; *Ber.* 1877, **10**, 188.

|| *J. Ind. Inst. Sci.* 1922, **5**, 163.

two fractions indicates that the alcohol was not homogeneous, a perusal of their memoir shows that the quantity of material subjected to fractionation was insufficient for a complete separation to have been effected. Sudborough and Rao suggest that the fusanols were secondary alcohols, but, since they react with phthalic anhydride in benzene solution, this is improbable.

Penfold has reinvestigated this so-called West Australian sandalwood oil and he has shown that it is doubtful if the two alcohols described by Sudborough and Rao actually exist. The alcohol fraction of the oil is a mixture of primary and secondary alcohols, which were separated by treatment with phthalic anhydride in benzene solution. The primary alcohol fraction contains a mixture of the santalols, identified by the preparation of the allophanate, m.p. $162-163^{\circ}$, together with a second alcohol, b.p. $160-161^{\circ}/4.5$ mm., d^{20}_{20} 0.942, n^{20}_D 1.5030, $\alpha_D + 5^{\circ}$. This alcohol has a lower density than the fusanols and it seems not improbable that they were a mixture of this alcohol and the santalols. The secondary alcohol was purified by conversion into its hydrogen phthalate at 140° ; it boiled at $146-150^{\circ}/1$ mm., d^{15}_{15} 0.995, n^{20}_D 1.5100, $\alpha_D + 27.2^{\circ}$. It gave no crystalline derivatives.

MACROCARPOL

The alcohol, *macrocarpol*, $C_{15}H_{26}O$, has been isolated by Briggs and Sutherland* from the essential oil present in the leaves and terminal branchlets of *Cupressus macrocarpa* growing in Auckland. The alcohol, which occurs in the fraction of the oil, b.p. $130-150^{\circ}/5$ mm., crystallised in tablets, m.p. 108° , $[\alpha]_D + 25.4^{\circ}$ (in alcohol) and it was characterised by the preparation of the α -*naphthylurethane*, m.p. $88-91^{\circ}$, and the 3:5-*dinitrobenzoate*, m.p. $157-158^{\circ}$. It would appear to be a saturated tricyclic alcohol but its structure has not been determined.

SESQUICAMPHENOL

In 1913 Semmler and Rosenberg† described the isolation from the high boiling fraction of camphor oil of a sesquiterpene alcohol, $C_{15}H_{26}O$, b.p. $159-162^{\circ}/7$ mm., d 0.9541, to which they gave the

* *J. Org. Chem.* 1942, 7, 397.

† *Ber.* 1913, 46, 770.

name *sesquicamphenol*. They furnished no evidence that it was homogeneous, but they prepared from it by dehydration with potassium hydrogen sulphate a *hydrocarbon*, $C_{15}H_{24}$, b.p. 125–130°/7 mm., $d_4^{20^\circ}$ 0.9138, n_D 1.50895, $[\alpha]_D + 50^\circ$. A more thorough investigation of the alcohol by Ruzicka and Stoll* has shown it to be a mixture consisting of a primary, two secondary and two tertiary alcohols.

The primary *alcohol*, which was separated from the secondary and tertiary alcohols by treatment with phthalic anhydride in benzene solution in the usual manner, was a colourless viscid oil, b.p. 158–159°/12 mm., $d_4^{14^\circ}$ 0.9516, $n_D^{14^\circ}$ 1.5020. It gave on catalytic hydrogenation a saturated *alcohol*, $C_{15}H_{28}O$, b.p. 152–153°/12 mm., $d_4^{22^\circ}$ 0.9150, $n_D^{22^\circ}$ 1.4755, remarkable for its low density and refractive index. The alcohol is probably tricyclic and it does not yield a naphthalene hydrocarbon on dehydrogenation with sulphur.

The mixture of secondary *alcohols*, isolated by the action of phthalic anhydride at 130°, boiled at 154–155°/12 mm., $d_4^{16^\circ}$ 0.9608, $n_D^{16^\circ}$ 1.5054, and consisted apparently of a mixture of two alcohols having the composition $C_{15}H_{26}O$ and $C_{15}H_{24}O$ respectively. By catalytic hydrogenation in the presence of platinum a saturated *alcohol*, $C_{15}H_{28}O$, b.p. 151–152°/12 mm., $d_4^{22^\circ}$ 0.9469, $n_D^{22^\circ}$ 1.4881, was obtained. Dehydrogenation of the mixture of unsaturated secondary alcohols with sulphur gave cadalene.

The alcohol fraction which did not react with phthalic anhydride was purified through the benzoate, and on hydrolysis gave a tertiary *alcohol*, b.p. 156°/12 mm., $d_4^{20^\circ}$ 0.9665, $n_D^{20^\circ}$ 1.5050. This fraction, in spite of its very constant boiling-point, is a mixture of at least two tertiary alcohols, since, on dehydrogenation with sulphur, both cadalene and eudalene are formed. The occurrence of derivatives of both these naphthalene hydrocarbons in the same oil is of interest.

SESQUICRYPTOL

The alcohol, *sesquicryptol*, $C_{15}H_{26}O$, m.p. 49–51°, b.p. 172–174°/20 mm., $d_4^{50^\circ}$ 0.9031, $n_D^{50^\circ}$ 1.4978, $[\alpha]_D^{22^\circ} + 22.7^\circ$ (in chloroform), occurs in the essential oil obtained from the leaves of

* *Helv. Chim. Acta*, 1924, 7, 260.

Cryptomeria japonica Don.* It is apparently a monocyclic primary alcohol containing two ethylenic linkages, since it gave on oxidation with chromic acid an aldehyde and with bromine a liquid tetrabromide. On dehydration with phosphorus pentoxide a *hydrocarbon*, $C_{15}H_{24}$, b.p. 250–255°/760 mm., $d_4^{25^\circ}$ 0.9078, $n_D^{25^\circ}$ 1.4980, $[\alpha]_D \pm 0^\circ$, was obtained which was probably tricyclic since it contained only one ethylenic linkage. No crystalline derivatives have been prepared from either the alcohol or hydrocarbon and their structures are unknown.

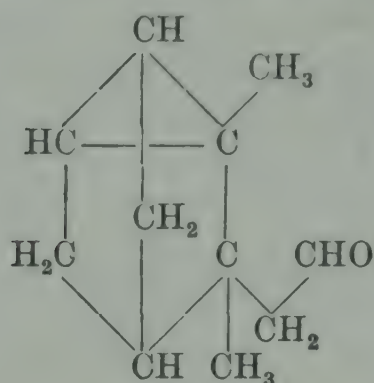
SESQUIGOYOL

The essential oil of *Pinus formosana* Hayata contains a crystalline sesquiterpene alcohol, *sesquigoyol*,† $C_{15}H_{26}O$, m.p. 137–137.5°, b.p. 160–165°/8 mm., $[\alpha]_D^{33^\circ} + 93.4$, *acetate*, b.p. 152–155°/4 mm., $[\alpha]_D^{32^\circ} + 22.2^\circ$. Sesquigoyol is probably dicyclic, since it was easily reduced by catalytic hydrogenation to *dihydrosesquigoyol*, m.p. 121°. It is of interest that the m.p. and optical rotatory power of sesquigoyol are in fair agreement with those recorded for partheniol (p. 164) and it is possible that the two alcohols are identical.

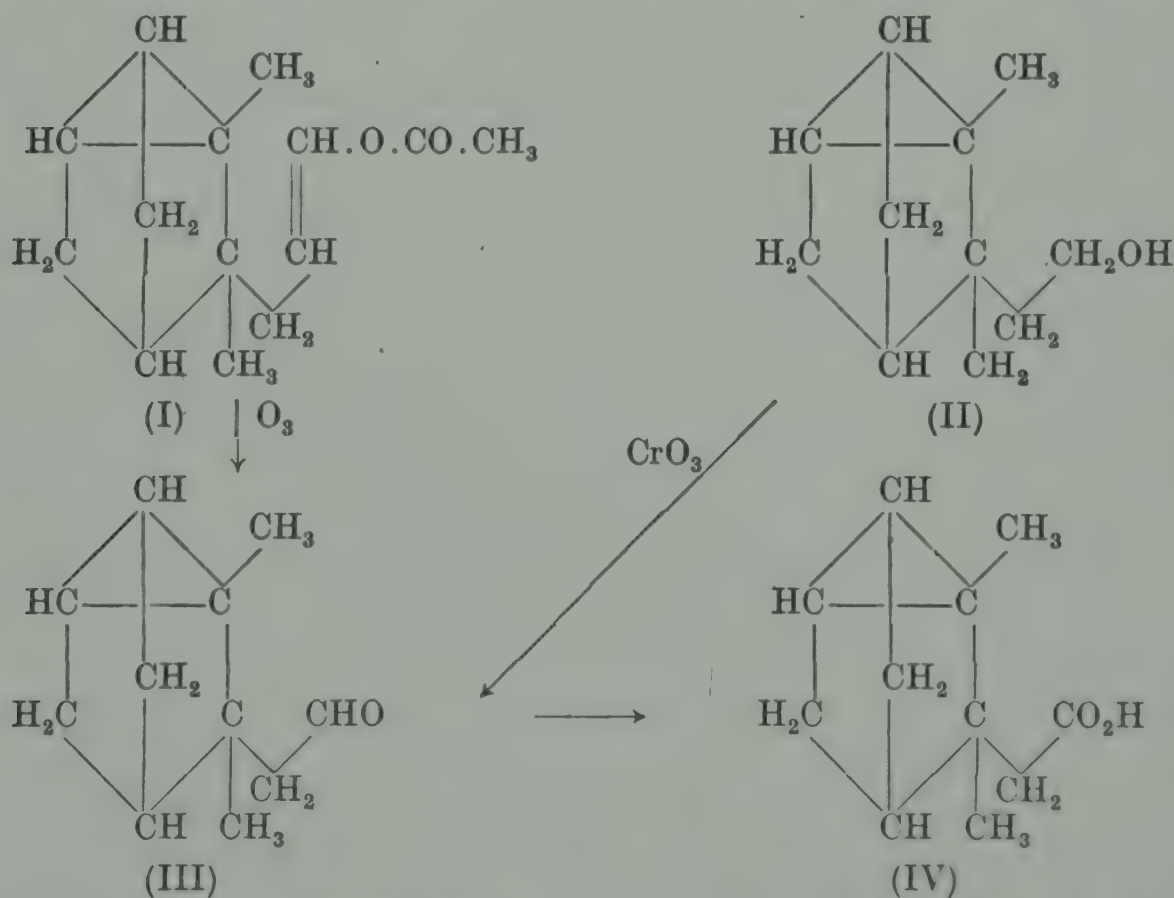
* Uchida and Murata, *J.S.C.I. Japan*, 1937, **40**, 159 B.

† Yeigai and Sabe, *J.C.S. Japan*, 1935, **56**, 1118.

CHAPTER III
ALDEHYDE
NORTRICYCLOEKASANTALAL



Chapoteaut* and Guerbet† noted the presence in East Indian sandalwood oil of an aldehyde, which was considered to have the composition $C_{15}H_{24}O$, and which gave a semicarbazone, m.p. 212° . The aldehyde was, however, first obtained pure by Schimmel and Co.‡ It was separated from the oil by the preparation of its bisulphite compound and was shown to have the composition $C_{11}H_{16}O$, b.p. $86-87^{\circ}/6\text{ mm.}$, $d^{20}_{20} 0.9938$, $n^{20}_D 1.4839$, $\alpha_D -38.48^{\circ}$.



* *Bull. Soc. chim.* 1882 [iii], 37, 303.

‡ *Schimmel's Report*, 1910, Oct., p. 124.

† *Compt. rend.* 1900, 130, 417.

It was characterised by the preparation of the *semicarbazone*, m.p. 223–224°, and there can be no doubt that it is identical with the aldehyde (III) prepared by Semmler* by the ozonolysis of the *enol-acetate* of *tricycloekasantalal* (I) (p. 100), and by Semmler and Zaar† by the oxidation of *nortricycloekasantalol* (II) with chromic acid.

The formula assigned to the natural aldehyde was confirmed by its oxidation to *nortricycloekasantalic acid* (IV).

The *oxime* is an oil, b.p. 135–137°/7 mm.

* *Ber.* 1909, **42**, 588.

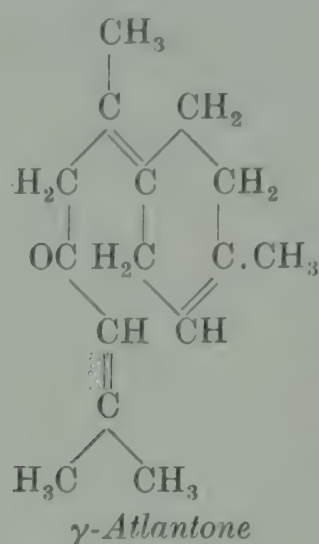
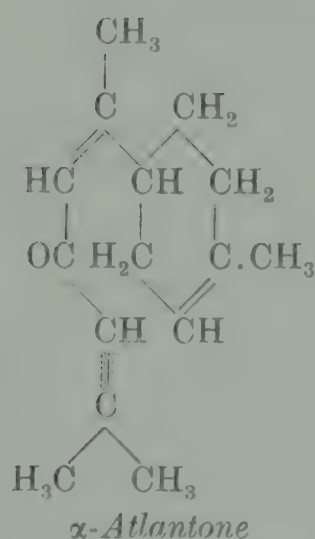
† *Ibid.* 1910, **43**, 1891.

CHAPTER IV

KETONES

A. MONOCYCLIC KETONES

THE ATLANTONES

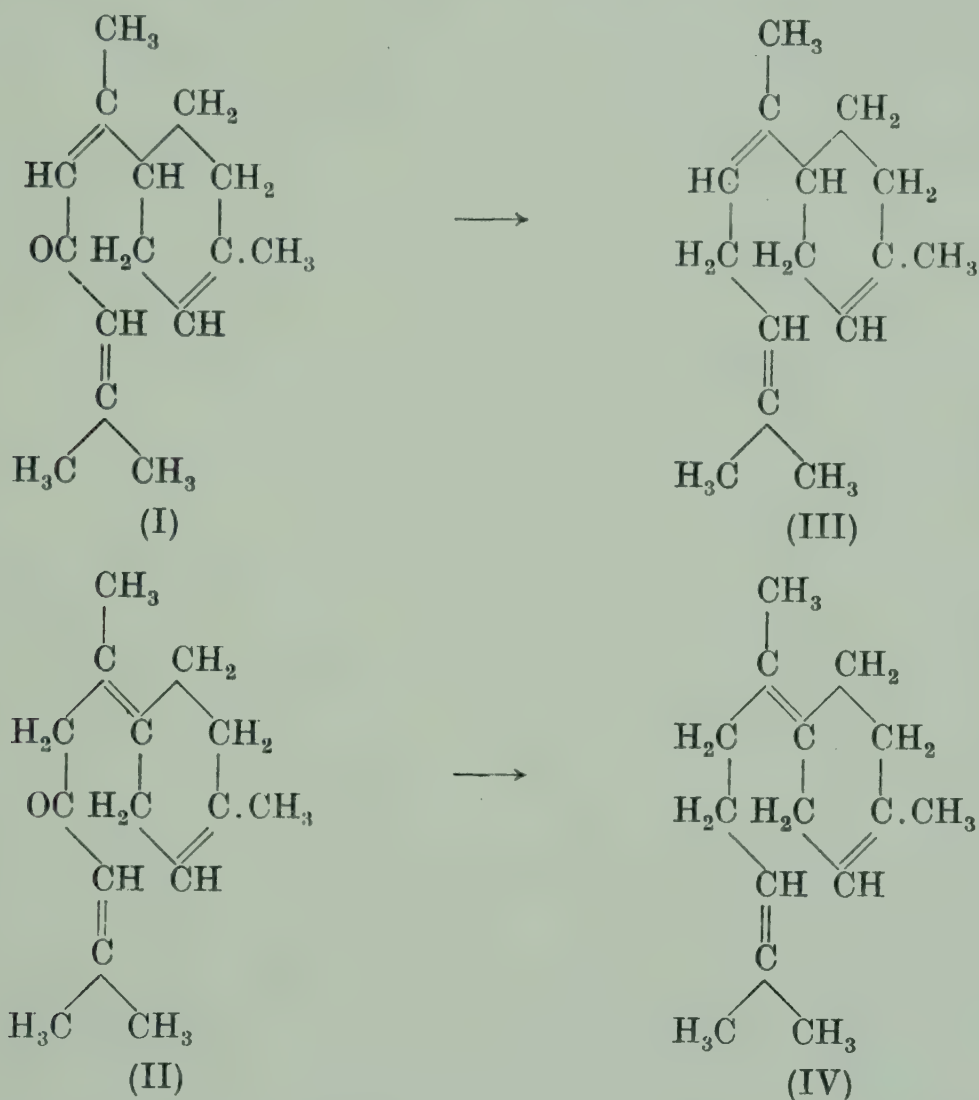


The two ketones, α - and γ -atlantones, $C_{15}H_{22}O$, have been found by Pfau and Plattner* to be present in the essential oils from the true cedar woods, *Cedrus libanotica* Link, *C. atlantica* Manet. and *C. Deodara* Loud. Since the two ketones do not yield any crystalline derivatives and their complete separation from the other constituents of the oils by chemical methods has not proved possible, they have not been isolated in the pure state. After treatment of the appropriate fraction of the oil with boric acid to remove the sesquiterpene alcohols present, the somewhat impure ketones had b.p. $119\text{--}122^\circ/1\text{ mm.}$, d^{20° 0.979 to 0.989, $n_D^{20^\circ}$ 1.513 to 1.523, $\alpha_D +1^\circ$ to $+6^\circ$. With semicarbazide, a vitreous *semicarbazido* derivative, $C_{16}H_{27}O_2N_3$, was obtained from which by hydrolysis with oxalic acid a somewhat purer mixture of ketones resulted, b.p. $121\text{--}123^\circ/1\text{ mm.}$, d^{20° 0.9562, $n_D^{20^\circ}$ 1.5181, $\alpha_D +2.5^\circ$. The oil, which was pale yellow in colour, had a faint sweet odour and readily resinified. It is not improbable that the pure ketones are optically inactive owing to equilibration, since the γ -form contains a plane of symmetry.

By an ingenious system of experiments, Pfau and Plattner showed that this ketonic fraction of the oil consisted of an

* *Helv. Chim. Acta*, 1932, 15, 1481; 1934, 17, 129.

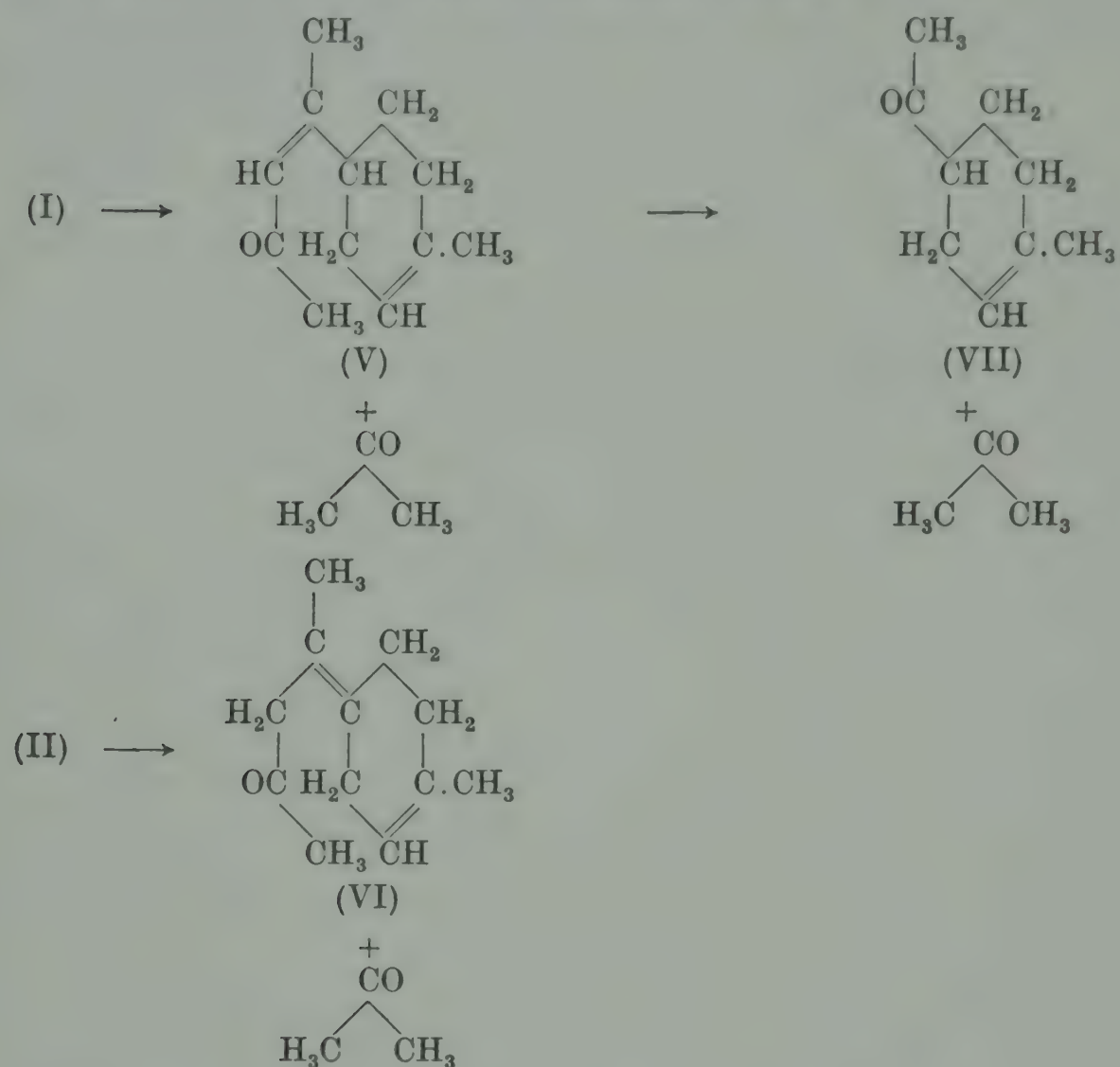
inseparable mixture of two ketones, α -atlantone (I) and γ -atlantone (II) derived respectively from α - and γ -bisabolenes (III) and (IV). By treatment of the semicarbazido derivative referred to above with potassium hydroxide a hydrocarbon was obtained which was identified as bisabolene by the preparation of the characteristic trihydrochloride, thus establishing the carbon skeleton of the ketones. This hydrocarbon consisted essentially of a mixture of α - and γ -bisabolenes.



For the determination of the positions of the ethylenic linkages a prolonged series of experiments was required, since ozonolysis of the ketones gave only acetone, formaldehyde and formic acid. No evidence was obtained of the presence of mesoxaldialdehyde which should have been formed from the α -ketone.

When the ketones were digested with dilute alcoholic potassium hydroxide the main products of the reaction were acetone and *acetyldipentene* (V), b.p. 125.5–126°/10 mm., d^{20}_D 0.9171, n^{20}_D 1.5044, *semicarbazone*, m.p. 152.5–153°. A second *semicarbazone*, m.p. 195–195.5°, derived probably from *acetylter-*

pinolene (VI) was also isolated. Treatment of the ketones with stronger alkali resulted in the formation of 1-methyl-4-acetyl- Δ^1 -cyclohexene (VII) (semicarbazone, m.p. 163°).



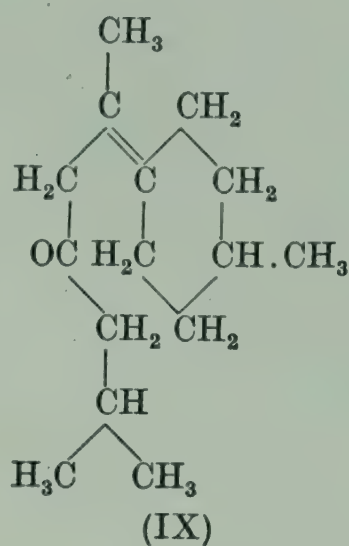
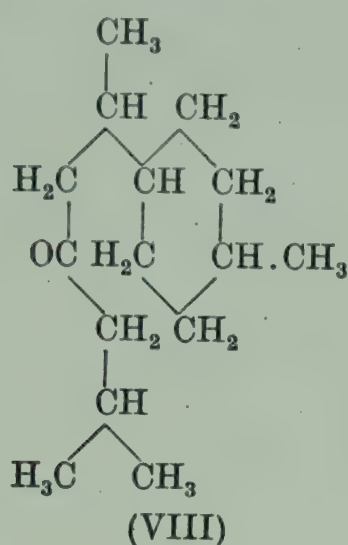
These experiments, which proved rigidly the presence and structure of α -atlantone, are of peculiar interest since previous investigations of cedarwood oil by Roberts* and by Simonsen and Rau† had recorded the presence of the *cyclohexenone* in the oil. It is now clear that this was an artefact and not an original constituent of the oil.

The presence of γ -atlantone was proved by a study of the products formed on reduction of the ketones. On catalytic hydrogenation in alcoholic solution at 70° using a nickel catalyst, absorption of between 2·3 and 2·8 molecules of hydrogen was observed, with the formation of a mixture of hexahydroatlantone and an unsaturated ketone. Removal of the latter by oxidation gave pure *hexahydroatlantone* (VIII), b.p. 147·5–148°/10 mm., d^{20}_D 0·8906, n^{20}_D 1·4598, $\alpha_D \pm 0^\circ$. It is probable that the un-

* *J.C.S.* 1916, 109, 791.

† *Ind. For. Rec.* 1922, 9, 13.

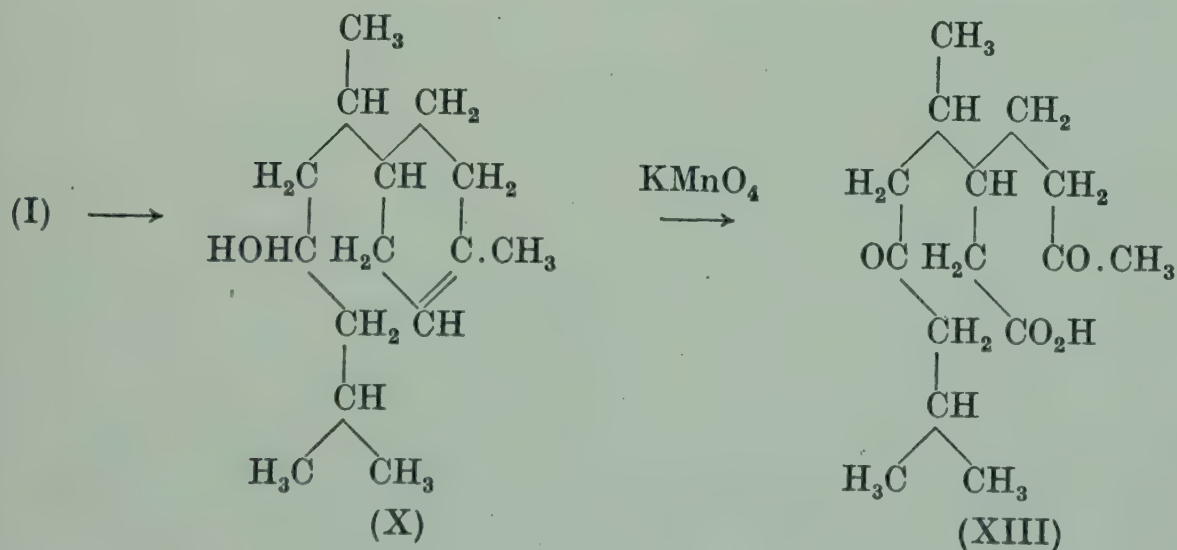
saturated ketone was *tetrahydro-γ-atlantone* (IX), the *exocyclic* ethylenic linkage not being reduced under the experimental conditions employed.

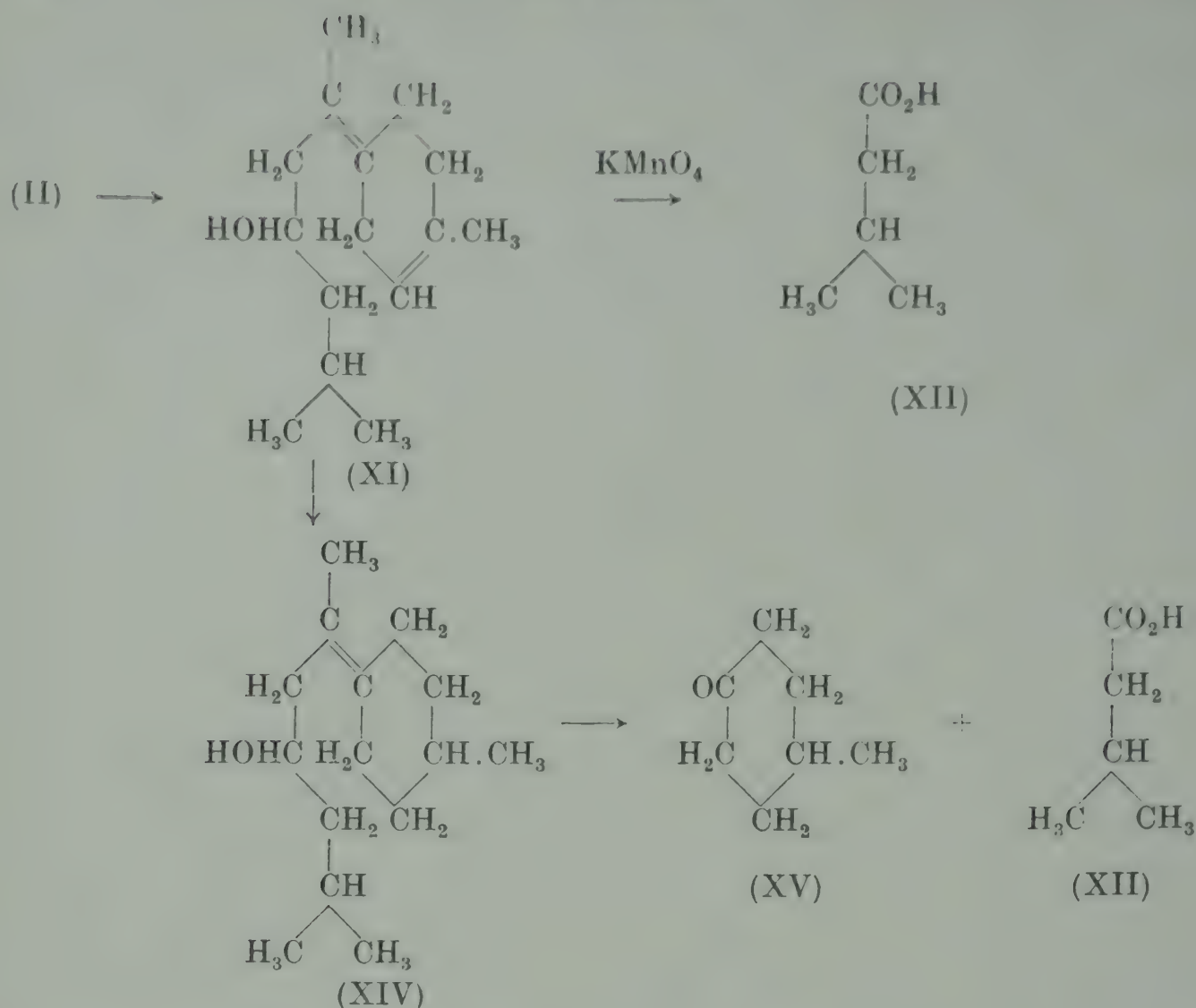


By reduction with sodium and alcohol a mixture, b.p. 158–160°/10 mm., d^{20}_D 0.9290, n^{20}_D 1.4892, $\alpha_D + 0.36^\circ$, of *tetrahydro-α-atlantol* (X) and *dihydro-γ-atlantol* (XI) was obtained which on oxidation with potassium permanganate gave *isovaleric acid* (XII) and a *diketocarboxylic acid*, C₁₅H₂₆O₄ (XIII), *methyl ester*, b.p. 165–167°/1 mm., n^{20}_D 1.4682, the latter being characterised by the preparation of a *semicarbazone*, m.p. 208–209°.

Rigid proof of the presence of the *alcohol* (XI), derived from *γ-atlantone*, in the mixture was provided by catalytic hydrogenation, which resulted in the formation of a mixture of *hexahydroatlantol* (VIII) and *tetrahydro-γ-atlantol* (XIV). Oxidation of this mixture of alcohols with potassium permanganate gave *isovaleric acid* (XII) and 4-*methylcyclohexan-1-one* (XV).

Whilst these elegant experiments have established the presence of *α*- and *γ*-atlantones as the main constituents of the





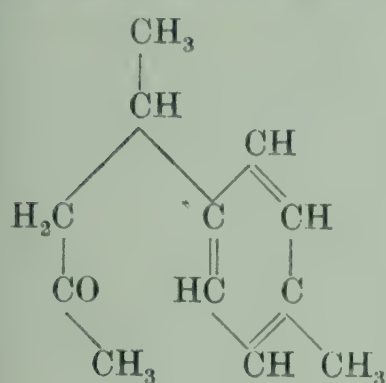
ketonic fraction of cedarwood oil, the fact that this yields on ozonolysis formaldehyde and formic acid, in addition to acetone, suggests the presence also of ketones containing an isopropenyl side chain.

TURMERONES

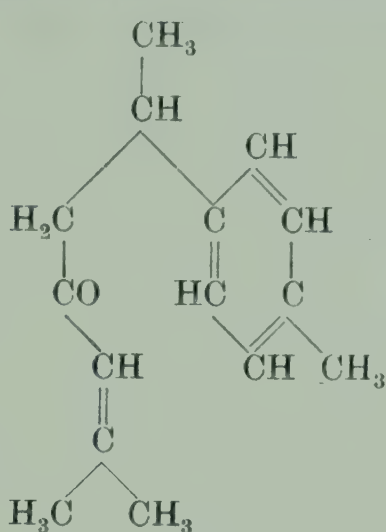
The essential oil from the rhizomes of *Curcuma longa* L. contains, as major component, a mixture of a monocyclic sesquiterpene ketone, $\text{C}_{15}\text{H}_{22}\text{O}$, called *turmerone* and a closely related aromatic ketone, $\text{C}_{15}\text{H}_{20}\text{O}$, called *ar-turmerone*.* Although turmerone has not as yet been obtained in a state of purity, its relationship to *ar-turmerone* has been clearly demonstrated and the structure of this latter ketone has been established unambiguously. On standing in air at room temperature the optical rotatory power of curcuma oil slowly became more dextro-rotatory. After some months the change was apparently com-

* Rupe, Clar, Pfau and Plattner, *Helv. Chim. Acta*, 1934, **17**, 372; Rupe and Gassman, *ibid.* 1936, **19**, 569; compare Kelkar and Rao, *J. Ind. Inst. Sci.* 1934, **17 A**, 7.

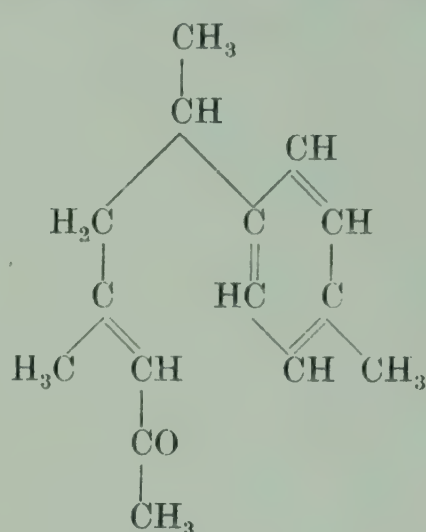
plete and on distillation pure *ar*-turmerone, b.p. 159–160°/10 mm., $d_4^{20^\circ}$ 0.9634, $n_D^{20^\circ}$ 1.5219, $[\alpha]_D + 82.2^\circ$, $[\alpha]_{5461} + 101.1^\circ$, was readily isolated. On hydrolysis with boiling aqueous-alcoholic caustic potash *ar*-turmerone furnished, in good yield, equimolecular amounts of *curcumone* (I), b.p. 115–117°/10 mm., $d_4^{20^\circ}$ 0.9620, $n_D^{20^\circ}$ 1.5046, $[\alpha]_D + 48.3^\circ$,* and acetone. This suggested the formula (II) for *ar*-turmerone, the alternative formula (III) being



(I)



(II)



(III)

discounted as *ar*-turmerone did not possess the properties of a methyl ketone. The presence of the exocyclic double bond in an isopropylidene residue was confirmed by ozonolysis. Rupe and Gassman[†] have developed an alternative and more expeditious method for the isolation of *ar*-turmerone from curcuma oil, by low-temperature chromic acid oxidation of the turmerone in the oil to *ar*-turmerone and preparation of the readily purified 2:4-dinitrophenylhydrazone, m.p. 133–4°, as intermediate. Other oxidising or dehydrogenating agents could also be applied, but were less satisfactory. *ar*-Turmerone was easily reduced with Raney nickel and hydrogen in alcohol solution to give a *dihydro-ar-turmerone* (IV), b.p. 146–147°/10 mm., $d_4^{20^\circ}$ 0.9384, $[\alpha]_D^{20^\circ} + 44.25^\circ$, $[\alpha]_{5461}^{20^\circ} + 54.3^\circ$. Racemic dihydro-*ar*-turmerone has been synthesised by Rupe and Gassman[‡] from β -methyl- β -(*p*-tolyl)-propionic acid. *ar*-Turmerone itself was obtained in very small yield by the same investigators when curcumone was condensed with acetone in alcoholic sodium ethoxide solution, and it has recently been synthesised by Colonge and Chambion.[§]

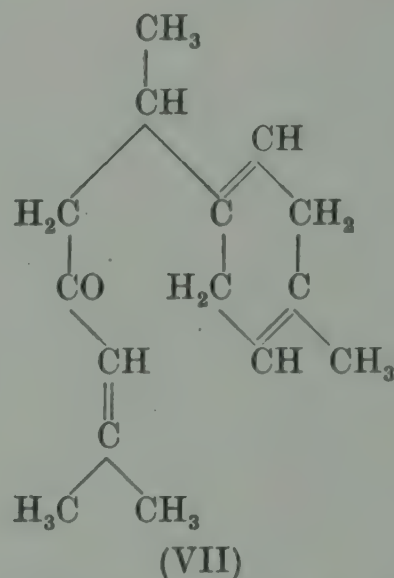
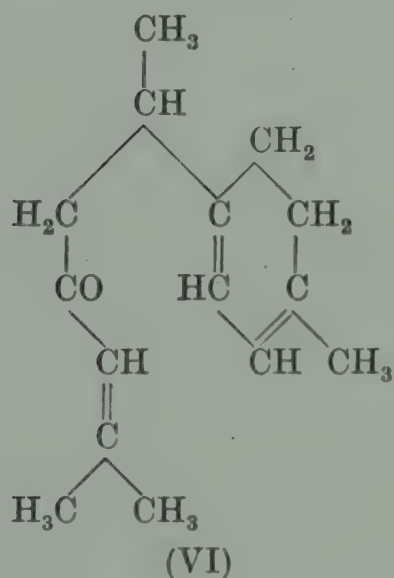
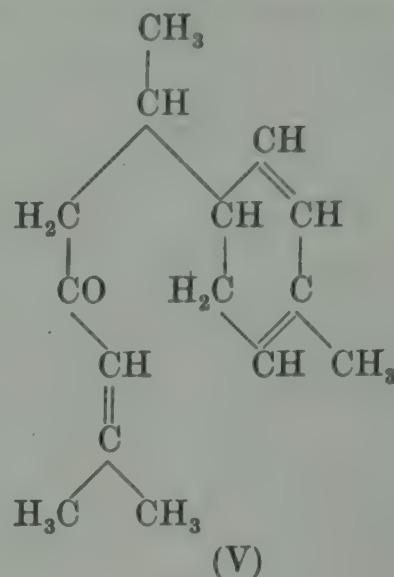
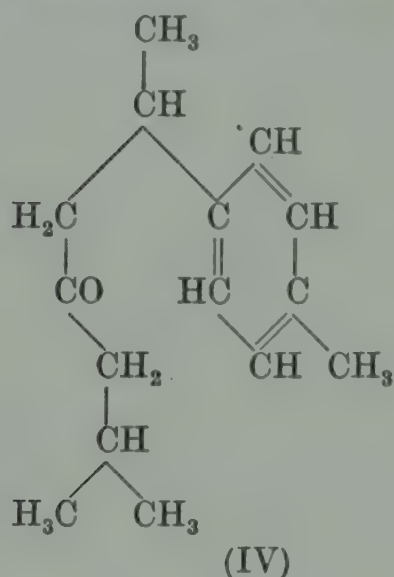
* For proof of structure see Rupe and Wiederkehr, *Helv. Chim. Acta*, 1924, **7**, 654.

[†] *Loc. cit.*

[‡] *Loc. cit.*

[§] *Compt. rend.* 1946, **222**, 557; see also Mukherjee, *J. Ind. C.S.* 1947, **24**, 341.

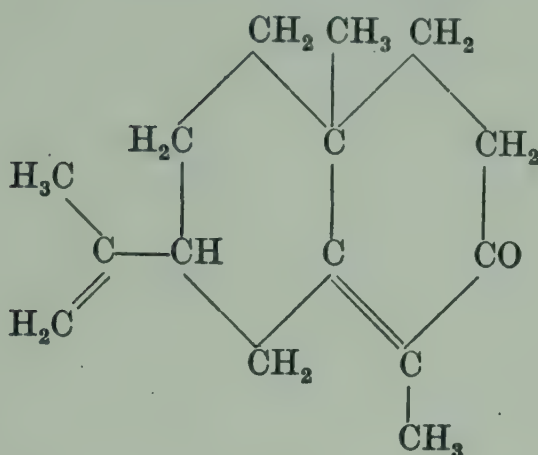
The formula $C_{15}H_{22}O$ for turmerone was indicated by a series of combustion analyses on the turmerone-*ar*-turmerone mixture of curcuma oil and on derivatives of this mixture. A typical impure turmerone fraction of the oil had b.p. 114–117°/10 mm., d_4^{20} 0.9502, n_D^{20} 1.5175, $[\alpha]_D + 13.8^\circ$. The formulae (V), (VI) and (VII), which were put forward as the best representative of



turmerone's reactions, follow from the ease of hydrolysis of turmerone to equimolecular amounts of an impure acetylmenthadiene and acetone and the ready formation of *ar*-turmerone by the action of oxidising agents. The Δ^1 position of the double bond in these turmerone formulae was suggested by analogy with examples in the monoterpene field. It is by no means certain, however, that the so-called turmerone may not be a mixture of several of these alternative formulae.

ar-Turmerone can be further characterised as the *semi-carbazone* m.p. 108–109°. No characteristic derivatives of turmerone have been prepared.

B. DICYCLIC KETONES

 α -CYPERONE

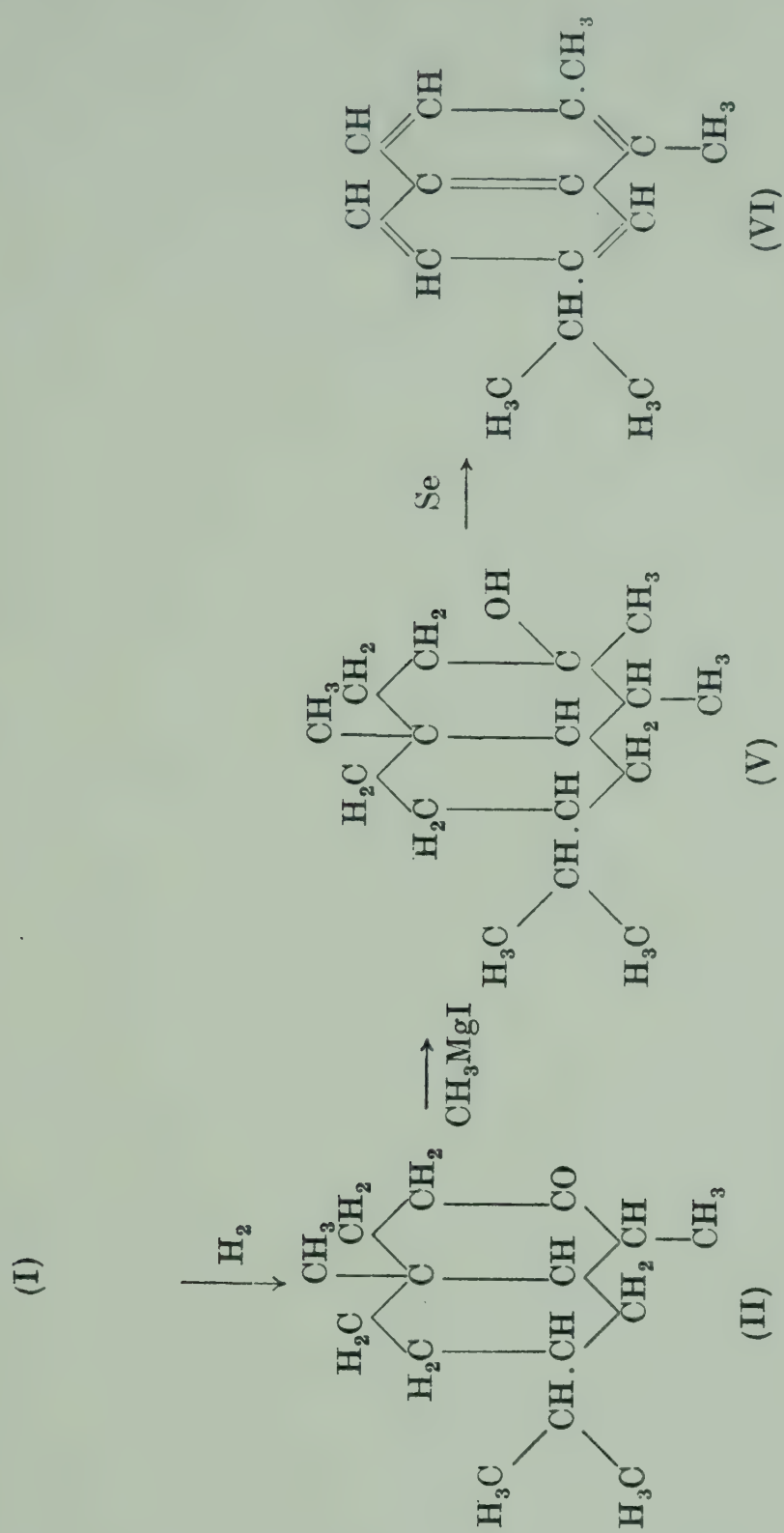
It was observed by Hegde and Rao* that the essential oil from the tubers of *Cyperus rotundus* contained a sesquiterpene ketone, α -cyperone, $\text{C}_{15}\text{H}_{22}\text{O}$. The constitution of this ketone was subsequently elucidated by the investigations of Bradfield, Gillam, Hegde, Rao and Simonsen,[†] and Bradfield, Pritchard and Simonsen.[‡]

The structure assigned to the ketone was based essentially on the evidence shown schematically on pp. 206, 207, which may be summarised as follows. α -Cyperone is a dicyclic ketone containing the *eudalene* (IX) skeleton and has two ethylenic linkages yielding on catalytic hydrogenation *tetrahydro- α -cyperone* (II). One of these ethylenic linkages is in the $\alpha:\beta$ -position to the carbonyl group as is shown by its absorption spectrum and by the fact that on reduction with sodium and alcohol the secondary alcohol, *dihydro- α -cyperol* (III) was obtained. The second ethylenic linkage must be *exocyclic* since ozonolysis of dihydro- α -cyperol gave formaldehyde and a keto-alcohol, from which a *diketone* (IV) (*dioxime*, decomp. $258-259^\circ$; *disemicarbazone*, decomp. $251-252^\circ$) was formed on oxidation with chromic acid. The carbonyl group was shown to be in position 2, since dehydrogenation with selenium of the *product* (V) prepared by the action of the Grignard reagent on tetrahydro- α -cyperone gave 1:2-dimethyl-7-isopropyl-naphthalene (VI). Proof of the position of the ethylenic linkage $\alpha:\beta$ - to the carbonyl group was furnished by the reduction and dehydrogenation of *hydroxymethylene- α -cyperone* (VII) to 1:3-

* J.S.C.I. 1935, 54, 387 T.

† J.C.S. 1936, p. 667.

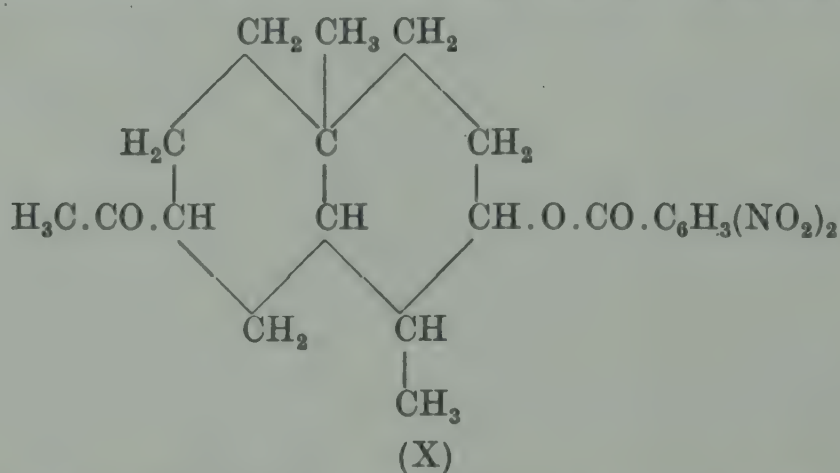
‡ Ibid. 1937, p. 760.



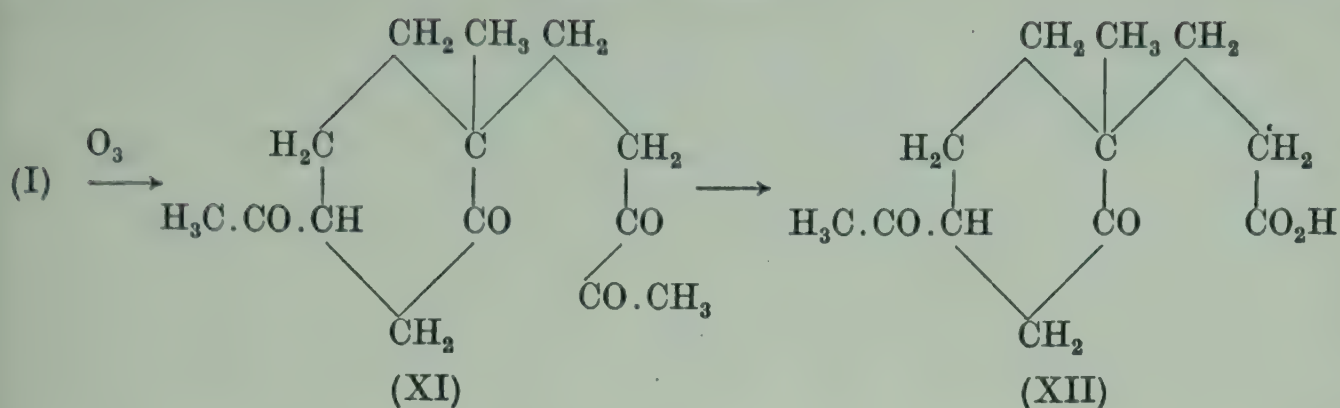
dimethyl-7-isopropyl-naphthalene (VIII). A synthetic confirmation of the structure (I) is given later on p. 210.

α -Cyperone is a colourless mobile oil, b.p. $177^{\circ}/20$ mm., $d_{25}^{25^{\circ}} 0.9946$, $n_D^{25^{\circ}} 1.5283$, $[\alpha]_{5461} + 138^{\circ}$, $[\alpha]_{5780} + 118.6^{\circ}$. It has been characterised by the preparation of a number of derivatives: *oxime*, m.p. 150.5° , $[\alpha]_{5461} + 134^{\circ}$ (in alcohol), *semicarbazone*, m.p. 216° , $[\alpha]_{5461} + 178^{\circ}$ (in chloroform), *2:4-dinitrophenylhydrazone*, m.p. $209-210^{\circ}$, *nitroguanylhyazone*, m.p. $203-204^{\circ}$, $[\alpha]_D + 196^{\circ}$ (in chloroform). Hydroxymethylene- α -cyperone (*2:4-dinitrophenylhydrazone*, m.p. $159-160^{\circ}$) was an oil, giving a reddish violet colour with alcoholic ferric chloride. Treatment of α -cyperone semicarbazone with sodium ethoxide gave a hydrocarbon, α -cyperene, b.p. $132-133^{\circ}/15$ mm., which was not reduced by sodium and alcohol.

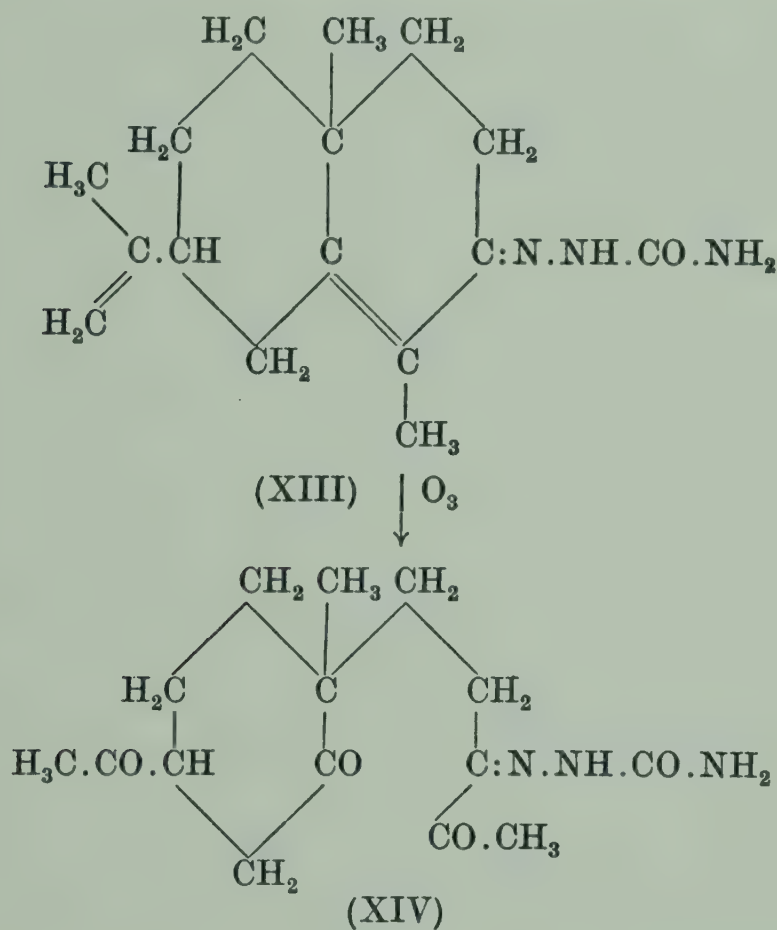
Tetrahydro- α -cyperone prepared by the catalytic hydrogenation of α -cyperone was a mobile oil, b.p. $151-152^{\circ}/14$ mm., $d_{25}^{25^{\circ}} 0.9597$, $n_D^{25^{\circ}} 1.4871$, $[\alpha]_{5461} + 14.8^{\circ}$, *oxime*, m.p. $116-117.5^{\circ}$, *semicarbazone*, m.p. $173-175^{\circ}$, *2:4-dinitrophenylhydrazone*, m.p. $151-152^{\circ}$. Its hydroxymethylene-derivative (*2:4-dinitrophenylhydrazone*, m.p. $182-183^{\circ}$) was an oil. Dihydro- α -cyperol, prepared by the reduction of α -cyperone with sodium and alcohol, was a very viscid oil, b.p. $167-168^{\circ}/15$ mm., $n_D^{25^{\circ}} 1.5121$, $[\alpha]_{5461} + 17.7^{\circ}$ (in alcohol); *3:5-dinitrobenzoate*, m.p. $157-158^{\circ}$. Ozonolysis of the dinitrobenzoate gave a crystalline *ketone*, $C_{21}H_{26}O_7N_2$, m.p. $148-149^{\circ}$, which is undoubtedly represented by (X), since it gave bromoform on further oxidation with sodium hypobromite.



Oxidation of α -cyperone with ozone furnished formaldehyde and a liquid acid, the methyl ester of which gave a *semicarbazone*, m.p. $245-246^{\circ}$. The *acid* is probably represented by (XII), being formed from the primary product of the oxidation (XI).

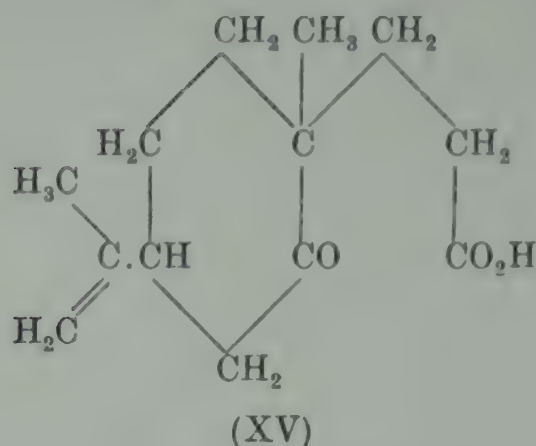


Further evidence in support of the formulation (I) for α -cyperone was afforded by the ozonolysis of α -cyperone semicarbazone (XIII) when a crystalline *semicarbazone*, $C_{15}H_{23}O_4N_3$, m.p. 185–187°, was obtained which was clearly (XIV).



Unlike eremophilone (compare p. 214) α -cyperone did not give an oxide when oxidised with hydrogen peroxide in alkaline solution but a *keto-acid*, $C_{13}H_{20}O_3$, m.p. 112°, $[\alpha]_{5461} + 62.6^\circ$, *semicarbazone*, m.p. 180–181°, *phenylsemicarbazone*, m.p. 200°. This acid was probably 1-methyl-4-isopropenylcyclohexan-2-one-1- β -propionic acid (XV).

α -Cyperone has the somewhat unusual property of being remarkably readily isomerised by digestion with either oxalic acid or methyl alcoholic potassium hydroxide. The isomeride,



β -cyperone, is an oil, b.p. 175–176°/16 mm., d_{25}^{25} 0.9945, n_D^{25} 1.5414, $[\alpha]_{5461} + 239^\circ$, *oxime*, m.p. 138°, $[\alpha]_{5461} + 217^\circ$ (in alcohol), *semicarbazone*, m.p. 207°, 2:4-dinitrophenylhydrazones, m.p. 218–219°, nitroguanylhyazone, m.p. 197°. β -Cyperone is a stereoisomeride of α -cyperone, since ozonolysis of β -cyperone semicarbazone yielded the same product (XIV) as was obtained from α -cyperone semicarbazone. This stereoisomerism can only lie in the relative disposition of the angular methyl group and the isopropenyl group, and the facility of the isomerisation is therefore remarkable.*

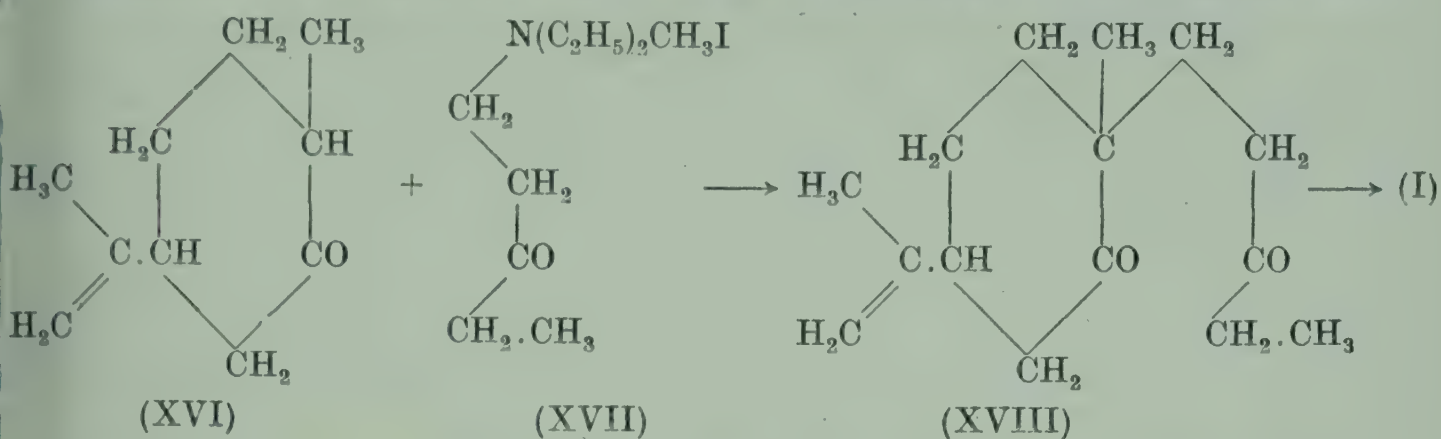
Whilst the evidence outlined above would appear to leave little doubt that the cyperones are correctly represented by (I), this formula is dependent in part on the unproved assumption that the methyl group eliminated on the dehydrogenation of dihydro- α -cyperol is in position 10. Confirmatory proof that this assumption is correct has been furnished by the synthetical experiments of Adamson, McQuillin, Robinson and Simonsen.† Ketones identical probably with α - and β -cyperones have been synthesised.

By the cyclisation with sodium ethoxide of 1-methyl-1- γ -ketopentyl-4-isopropenyl-cyclohexan-2-one (XVIII), prepared by the interaction of 1-dihydrocarvone (XVI) and diethylaminopentan-3-one methiodide (XVII), a ketone was obtained which was probably structurally identical with the cyperones (I). The oxime prepared from this ketone was, morphologically, practically identical with the oxime of the natural α -cyperone. If the cyclisation was carried out with sulphuric acid the ketone ob-

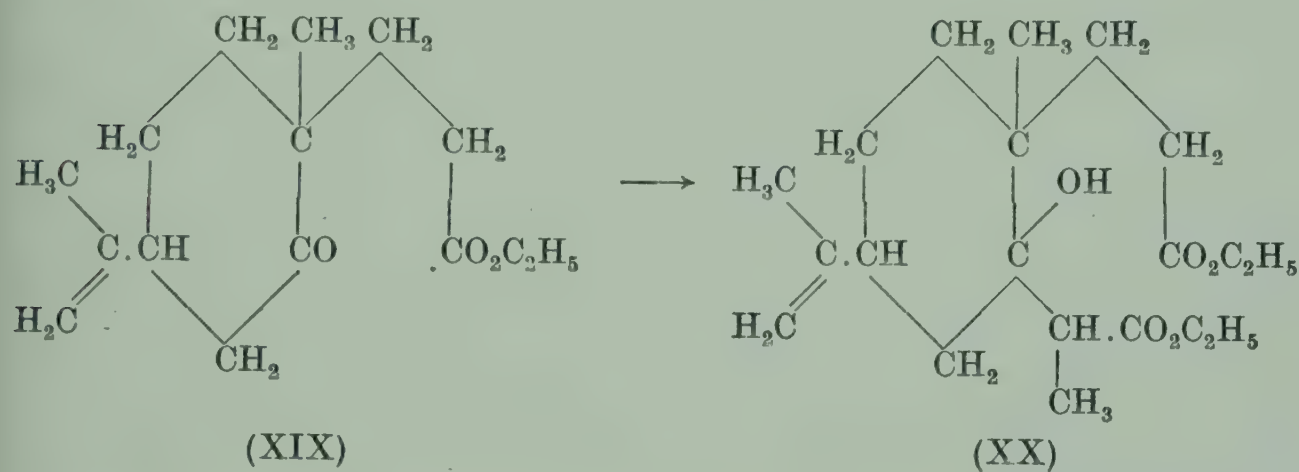
* McQuillin (*J.C.S.* 1951, in the press) has very recently suggested an alternative formula for β -cyperone.

† *J.C.S.* 1937, p. 1576; compare Bradfield, Jones and Simonsen, *ibid.* 1936, p. 1137.

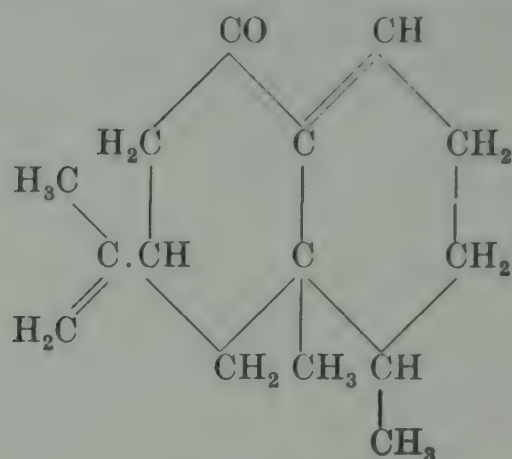
tained resembled β -cyperone, although here, as in the case of the synthetic α -cyperone, divergences in the melting-points of the natural and synthetic ketones were observed. A synthetic ketone resembling and probably identical with β -cyperone was prepared



also by the condensation of *ethyl 1-methyl-4-isopropenyl-cyclohexan-2-one-1- β -propionate* (XIX) with ethyl α -bromopropionate in the presence of zinc. From the product (XX) of the condensation, a ketone resembling β -cyperone was isolated; after reduction with sodium and alcohol it gave a *decalol*, b.p. $160^\circ/12$ mm., n_D^{25} 1.5032, the 3:5-dinitrobenzoate of which had m.p. 150 – 152° and which in admixture with dihydro- α -cyperyl-3:5-dinitrobenzoate had m.p. 150 – 153° .



A consideration of these experiments leaves little doubt that the synthetic ketones were structurally identical with the natural compounds, the position being complicated by ready, though not necessarily complete, racemisation. The importance of this synthetical work lies undoubtedly in that it provided the first definite proof of the position of the angular methyl group in sesquiterpenes yielding eudalene on dehydrogenation.

EREMOPHILONE

The tall shrub or small tree, *Eremophila Mitchelli*, known vernacularly as buddah wood, bastard sandalwood or budtha, occurs in the drier parts of New South Wales, Queensland and South Australia. The wood on distillation in steam yields from two to three per cent. of an extremely viscid reddish brown oil with a characteristic sweetish odour. A prolonged investigation of the oil by Penfold, Simonsen and their collaborators* has shown it to contain three closely related crystalline ketones, *eremophilone*, $C_{15}H_{22}O$, *hydroxyeremophilone*, $C_{15}H_{22}O_2$, and *hydroxydihydroeremophilone*, $C_{15}H_{24}O_2$. Their separation afforded very considerable difficulties.

The method adopted originally was to digest the oil with aqueous sodium bisulphite with which *eremophilone* and *hydroxyeremophilone* combined to yield soluble derivatives, *hydroxydihydroeremophilone* not reacting with this reagent. By fractional decomposition of the bisulphite compounds with sodium hydroxide, *eremophilone* and *hydroxyeremophilone* were separated, but the process was wasteful owing to the formation of soluble sulphonates. A more convenient method was found to be the treatment of a pyridine solution of the oil with benzoyl chloride, when *hydroxyeremophilone* gave a crystalline benzoate (see below) which was readily separated from *eremophilone* owing to its sparing solubility in ligroin; the latter ketone was then purified by distillation under diminished pressure.

* Bradfield, Penfold and Simonsen, *J.C.S.* 1932, p. 2744; *Proc. Roy. Soc. New South Wales*, 1933, 66, 420; Bradfield, Hellström, Penfold and Simonsen, *J.C.S.* 1938, p. 767; Adamson, Marlow and Simonsen, *ibid.* p. 774; Penfold and Simonsen, *ibid.* 1939, p. 87; Copp and Simonsen, *ibid.* 1940, p. 415; Gillam, Lynas-Gray, Penfold and Simonsen, *ibid.* 1941, p. 60.

Eremophilone crystallised in colourless needles, m.p. 41–42°, b.p. 171°/15 mm., $d_{25}^{25^\circ}$ 0.9994, $n_D^{25^\circ}$ 1.5182, $[\alpha]_{5461}$ –207°. It oxidised somewhat readily and passed into a yellow oil on exposure to the air. It was characterised by the preparation of its *semicarbazone*, m.p. 202–203°, $[\alpha]_{5461}$ –293° (in methyl alcohol).

Hydroxyeremophilone crystallised in prisms, m.p. 66–67°, b.p. 189–190°/22 mm., $d_{25}^{25^\circ}$ 1.062, $n_D^{25^\circ}$ 1.5564, $[\alpha]_{5461}$ +153° (in methyl alcohol). It resinified extremely rapidly on exposure to the air. Its absorption spectrum is discussed by Gillam.* The benzoate crystallised in stout prisms, m.p. 119–120°, $[\alpha]_{5461}$ +162° (in ethyl acetate).

Hydroxydihydroeremophilone crystallised in slender prisms, m.p. 102–103°, $[\alpha]_{5461}$ +94° (in methyl alcohol) and unlike the two ketones with which it occurs is not oxidised on exposure to the air. It yielded a number of crystalline derivatives: *diacetate*, m.p. 69–70°, *3:5-dinitrobenzoate*, m.p. 145–146°, *2:4-dinitrophenylhydrazone*, m.p. 239–241°.

Bradfield, Penfold and Simonsen† suggested that eremophilone, hydroxyeremophilone and hydroxydihydroeremophilone were represented respectively by (I), (II) and (III) and the salient facts upon which these structures were advanced may now be briefly summarised.

Eremophilone is a eudalene derivative since *dihydroeremophilol* (IV), b.p. 168–170°/14 mm., $n_D^{25^\circ}$ 1.5089, $[\alpha]_{5461}$ +68.8° (in methyl alcohol), *3:5-dinitrobenzoate*, m.p. 119–121°, prepared by reduction of the ketone with sodium and alcohol, gave eudalene (V) on dehydrogenation with selenium. Eremophilone contained two ethylenic linkages yielding on catalytic hydrogenation *tetrahydroeremophilone* (VI), b.p. 165°/17 mm., $d_{25}^{25^\circ}$ 0.9641, $n_D^{25^\circ}$ 1.4909, $[\alpha]_{5461}$ +12.5° (in methyl alcohol), *oxime*, m.p. 126–127.5°, $[\alpha]_{5461}$ +17.2° (in chloroform), *semicarbazone*, m.p. 213–214°, *2:4-dinitrophenylhydrazone*, m.p. 178–179°. It was deduced that one of the ethylenic linkages must be in the $\alpha:\beta$ -position to the carbonyl group on the evidence of (i) the absorption spectrum,‡ (ii) the formation of an unstable derivative with hydrogen sulphide, and (iii) by its oxidation with hydrogen peroxide in

* Gillam, *J.C.S.* 1936, p. 676.

‡ *Loc. cit.*

† *Loc. cit.*

alkaline solution to an oxide, *eremophilone oxide* (VII), m.p. 63–64°, $[\alpha]_{5461} - 208^\circ$ (in methyl alcohol). Further the presence of the group $-\text{CH}_2-\text{CO}-\text{CH}:\text{CH}-$ was established by the preparation of a *hydroxymethylene* derivative, m.p. 105°. Since dihydroeremophilol gave on ozonolysis formaldehyde and a liquid *keto-alcohol*, $\text{C}_{14}\text{H}_{24}\text{O}_2$ (VIII) (2:4-dinitrophenylhydrazone, m.p. 148–149°), which was oxidised by sodium hypobromite to a *hydroxy-acid*, $\text{C}_{13}\text{H}_{22}\text{O}_3$ (IX), m.p. ca. 155°, the second ethylenic linkage was present in an isopropenyl side chain.

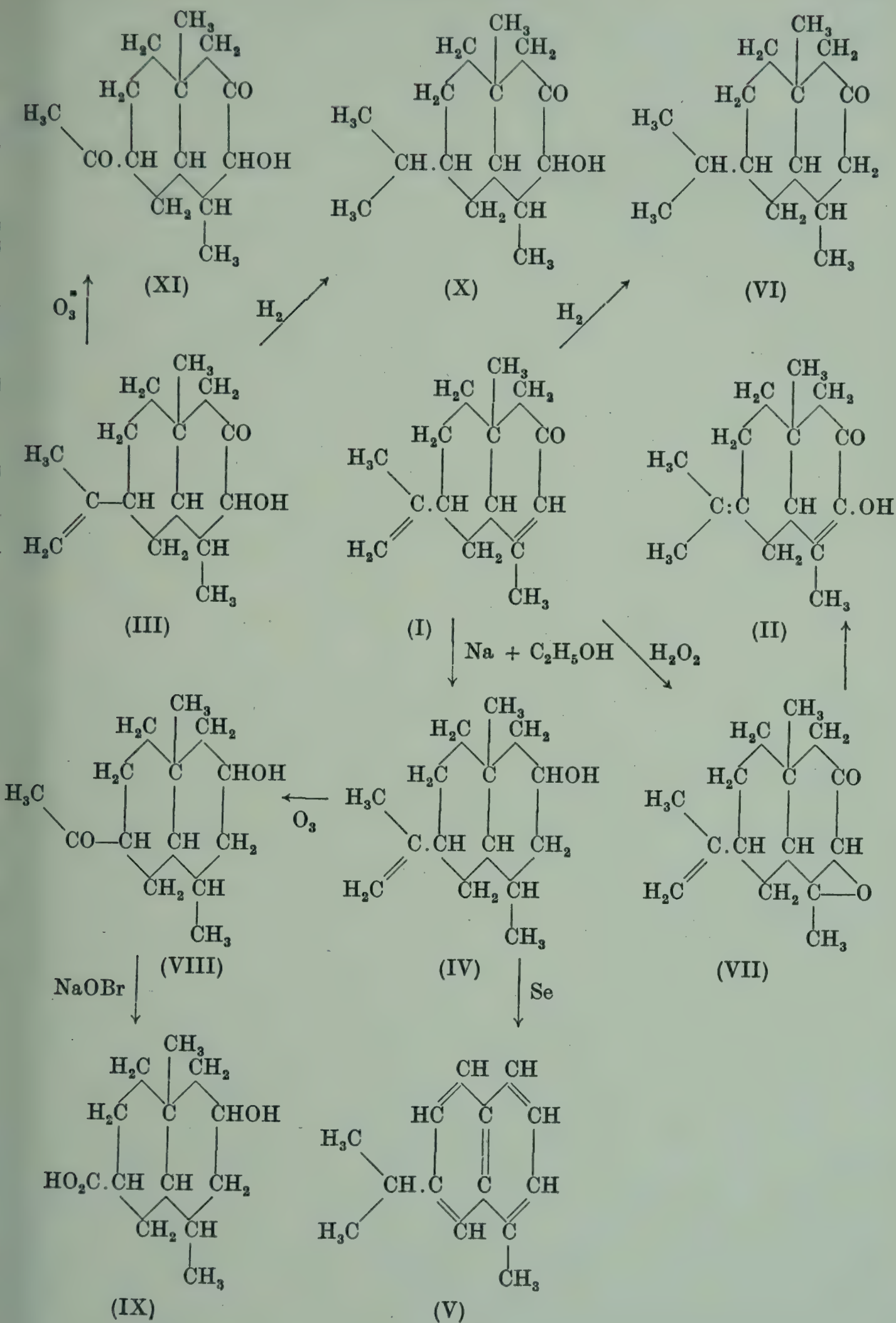
On the basis of formula (I) for eremophilone, hydroxyeremophilone was represented by (II), since its benzoate gave on ozonolysis, amongst other substances (see p. 217), acetone and no formaldehyde, indicating the presence of an isopropylidene side chain, whilst eremophilone oxide (VII), on digestion with acetic anhydride and sodium acetate followed by hydrolysis with alcoholic potassium hydroxide gave hydroxyeremophilone, the "synthetic" benzoate prepared from this having the same melting-point and rotatory power as the benzoate obtained from the natural product.

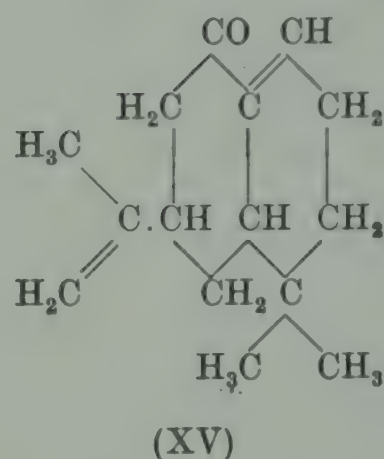
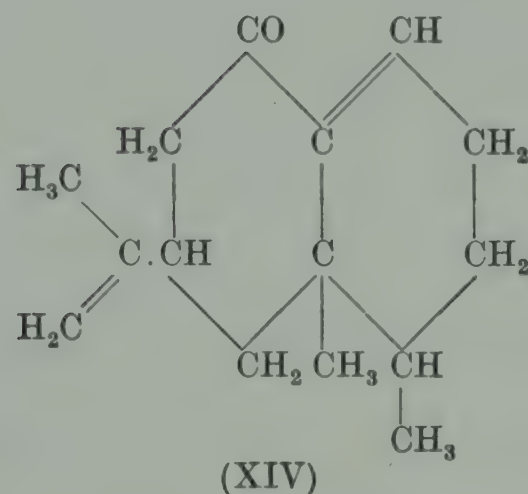
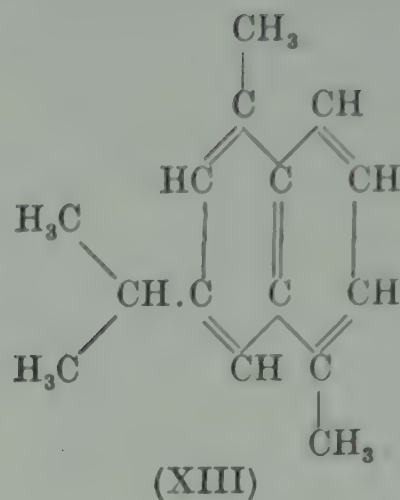
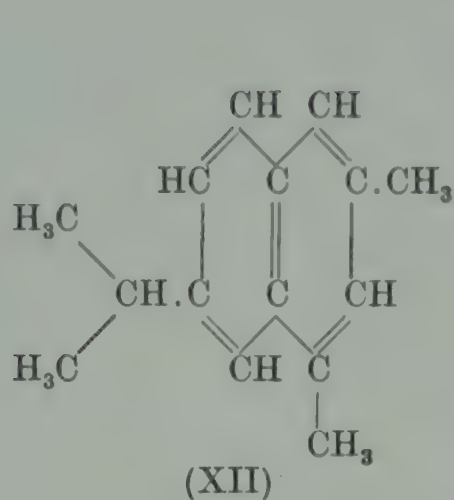
The representation of hydroxydihydroeremophilone by (III) was based upon the observations (i) that it gave on catalytic hydrogenation *hydroxytetrahydroeremophilone* (X), m.p. 84–85°, $[\alpha]_{5461} + 84.2^\circ$ (in methyl alcohol), *oxime*, m.p. 158–160°, 2:4-dinitrophenylhydrazone, m.p. 219–220°, yielding on reduction with sodium amalgam tetrahydroeremophilone (VI), and (ii) that on ozonolysis it gave formaldehyde and a liquid *diketo-alcohol*, $\text{C}_{14}\text{H}_{22}\text{O}_3$ (XI), *semicarbazone*, m.p. 216–219°.

The observation of Bradfield, Pritchard and Simonsen* that tetrahydroeremophilone furnished on treatment with methyl magnesium iodide, followed by dehydrogenation with selenium, not 1:3-dimethyl-7-isopropyl-naphthalene (XII), but 1:5-dimethyl-7-isopropyl-naphthalene (XIII), showed that tetrahydroeremophilone could not be represented by (VI) and that the carbonyl group in eremophilone and its congeners must be in position 5 and not 3 as had been assumed.

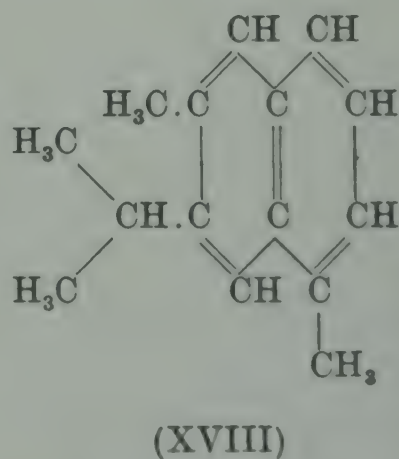
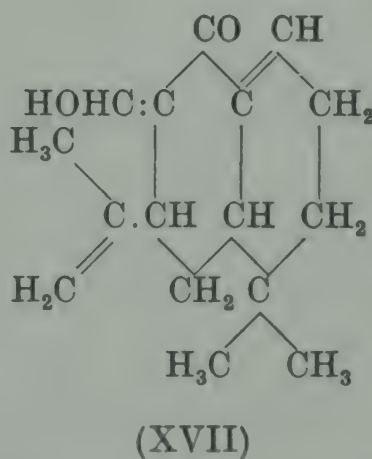
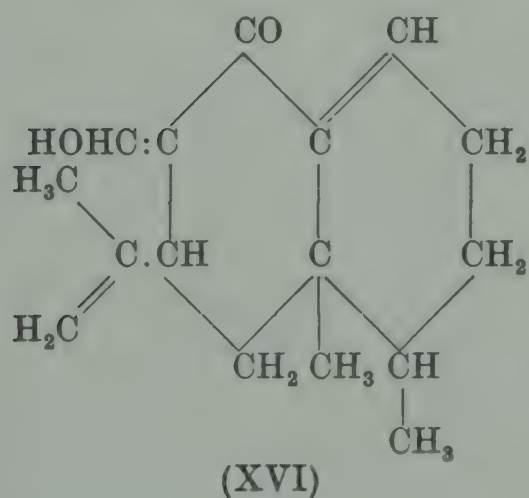
Since, as mentioned above, it had been proved conclusively that eremophilone contained the grouping $-\text{CH}_2-\text{CO}-\text{CH}:\text{CH}-$,

* *J.C.S.* 1937, p. 760; compare Bradfield, Hegde, Rao, Simonsen and Gillam, *ibid.* 1936, p. 667.



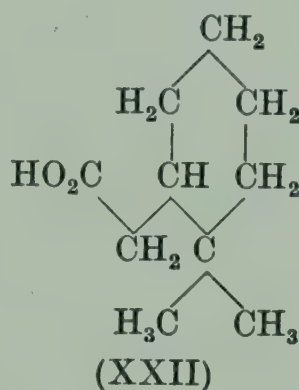
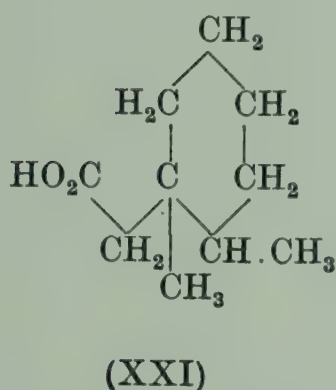
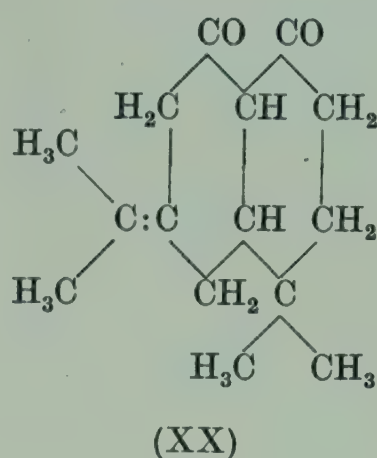
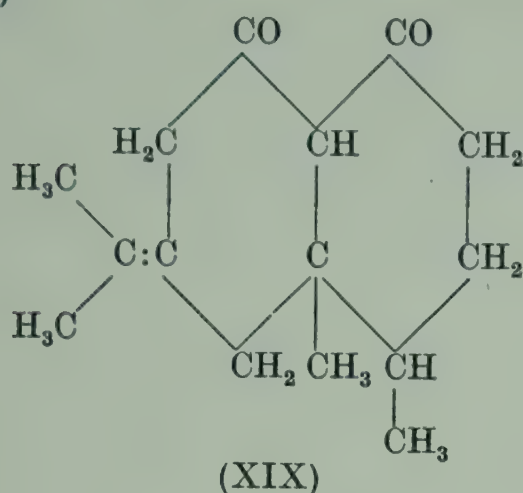


it was obvious that the methyl extruded on selenium dehydrogenation could not be in position 10 and was most probably in one of the alternative positions 1 or 9 leading to formulae (XIV) or (XV) for eremophilone. Confirmation of the position of the methylene group at C₆ was obtained by hydrogenation of hydroxymethylene eremophilone, (XVI) or (XVII), followed by dehydrogenation with selenium to 1:6-dimethyl-7-isopropyl-naphthalene (XVIII).



On the basis of the alternative representations (XIV) and (XV) for eremophilone it appeared probable that hydroxyeremophilone

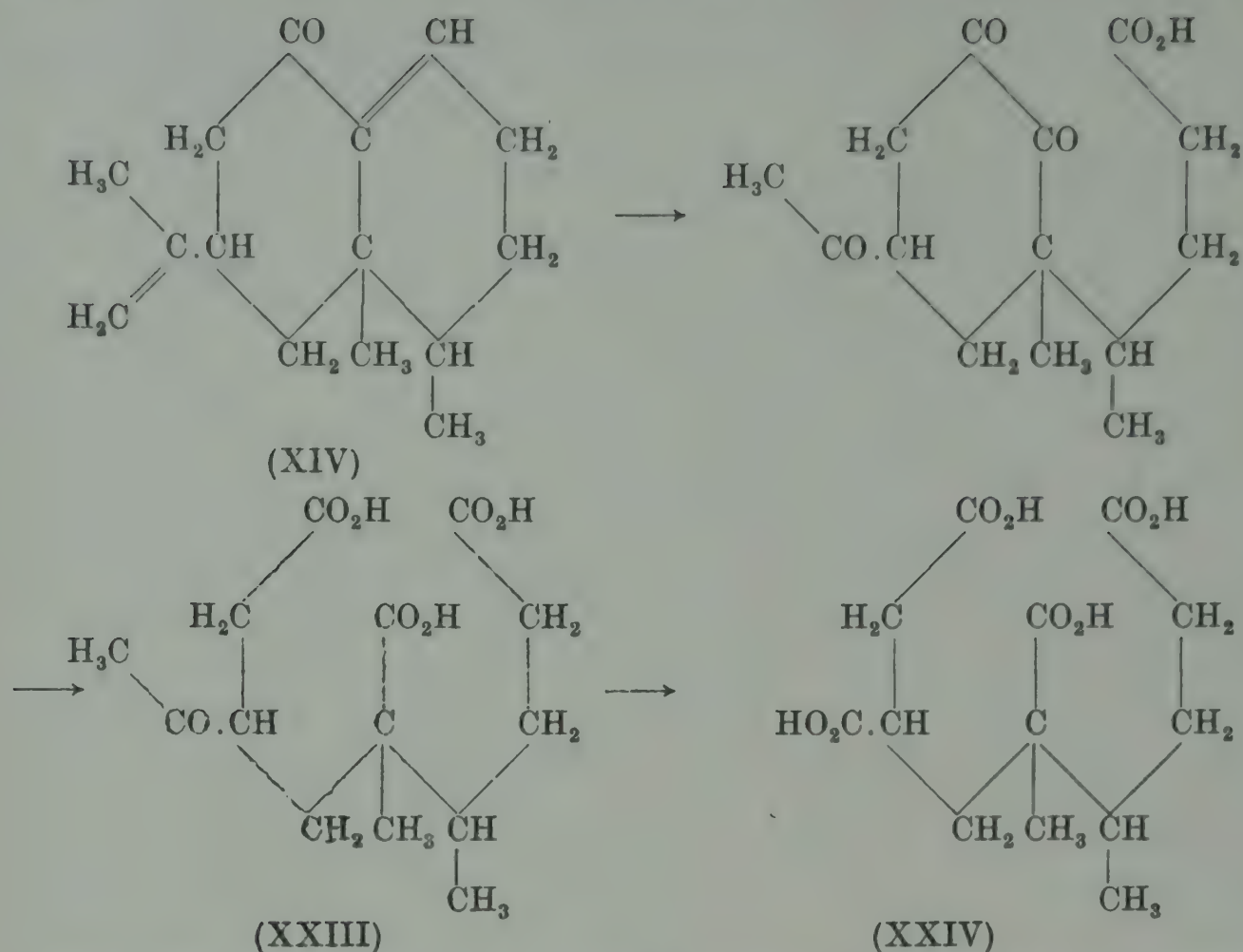
was one of the enolic modifications of the diketones (XIX) or (XX).



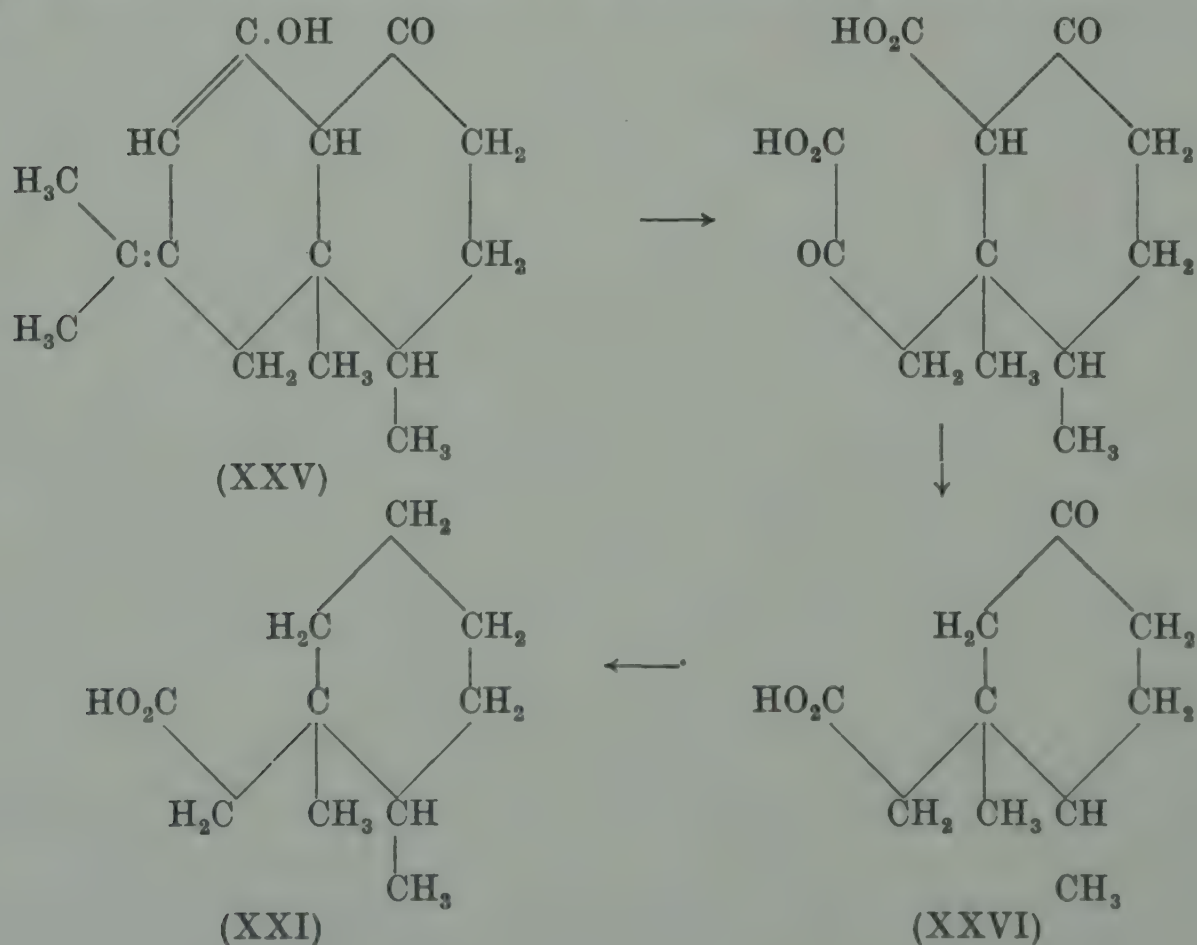
It was mentioned above (p. 214) that on ozonolysis the benzoate of hydroxyeremophilone gave acetone; in addition two crystalline products were obtained, an *oxide*, $C_{19}H_{20}O_5$, m.p. $188-189^\circ$, and a *keto-acid*, $C_{10}H_{16}O_3$, m.p. $103-105^\circ$, $[\alpha]_{5461} + 28.3^\circ$ (in methyl alcohol), *semicarbazone*, m.p. $208-209^\circ$. Reduction of this keto-acid with zinc and hydrochloric acid gave a liquid acid, $C_{10}H_{18}O_2$; *p*-phenylphenacyl ester, m.p. $65-67^\circ$, $[\alpha]_{5461} + 15.3^\circ$ (in ethyl acetate), which if derived from an enolic form of (XIX) or (XX) would be represented by either (XXI) or (XXII). Acids represented by these two formulae were synthesised, resolved into their optical enantiomorphs and their *p*-phenylphenacyl esters prepared.* Direct comparison showed that (XXI) correctly represented the acid derived from the benzoate.

From this it was deduced that eremophilone must be represented by (XIV) and additional proof that this was correct was furnished by its ozonolysis, when a liquid keto-acid was obtained, probably represented by (XXIII), since it gave on further oxidation with sodium hypobromite a *tetrabasic acid*, $C_{13}H_{20}O_8$ (XXIV).

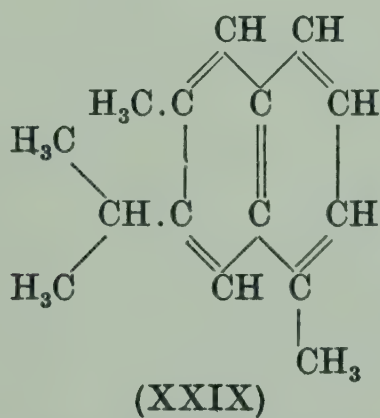
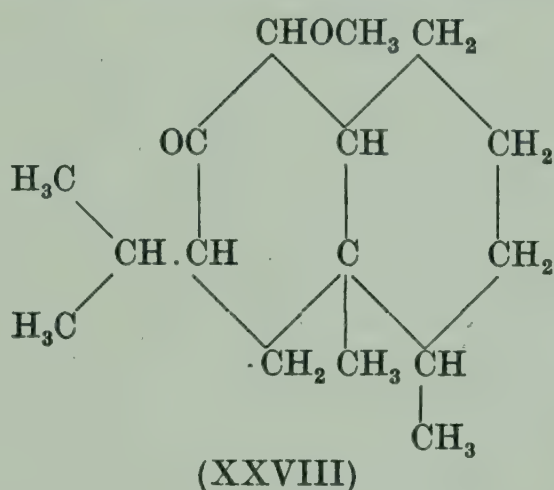
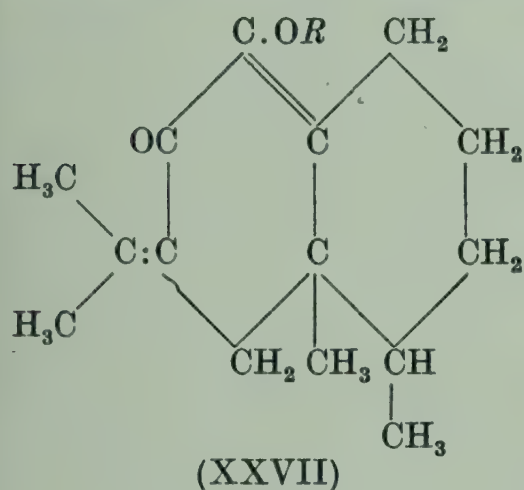
* Adamson, Marlow and Simonsen; Copp and Simonsen (*loc. cit.*)



Whilst the experiments which have been outlined above established the structure of eremophilone, the position of the hydroxy group in hydroxyeremophilone remained to be determined. The degradation of the benzoate to the methylcyclohexylacetic acid

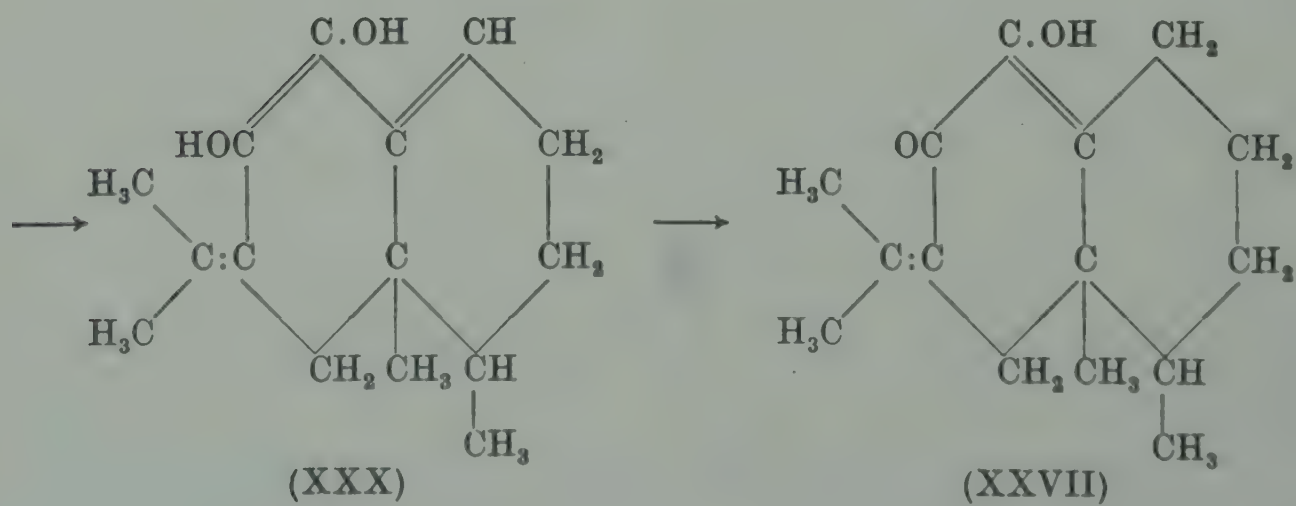
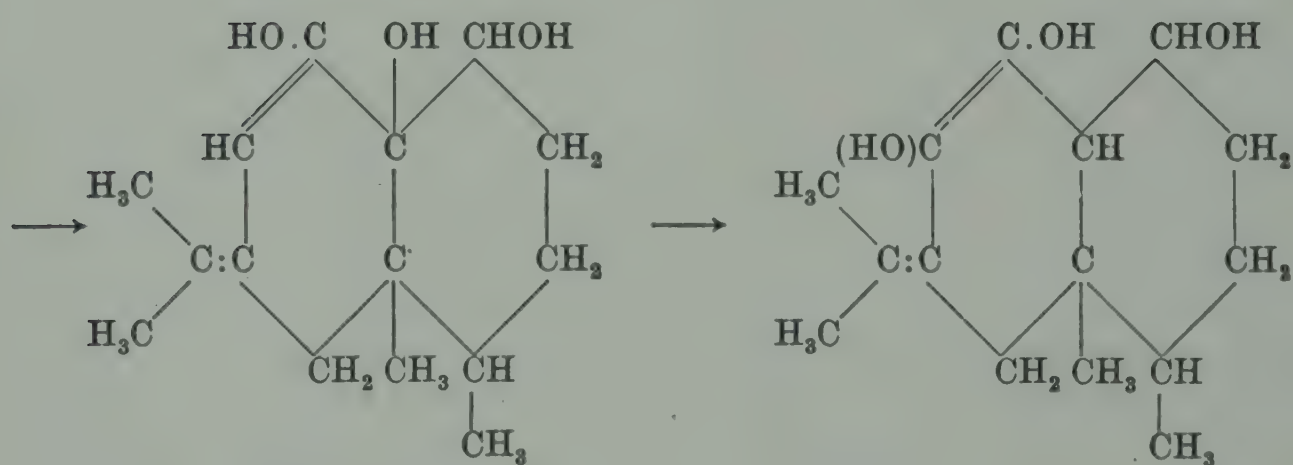
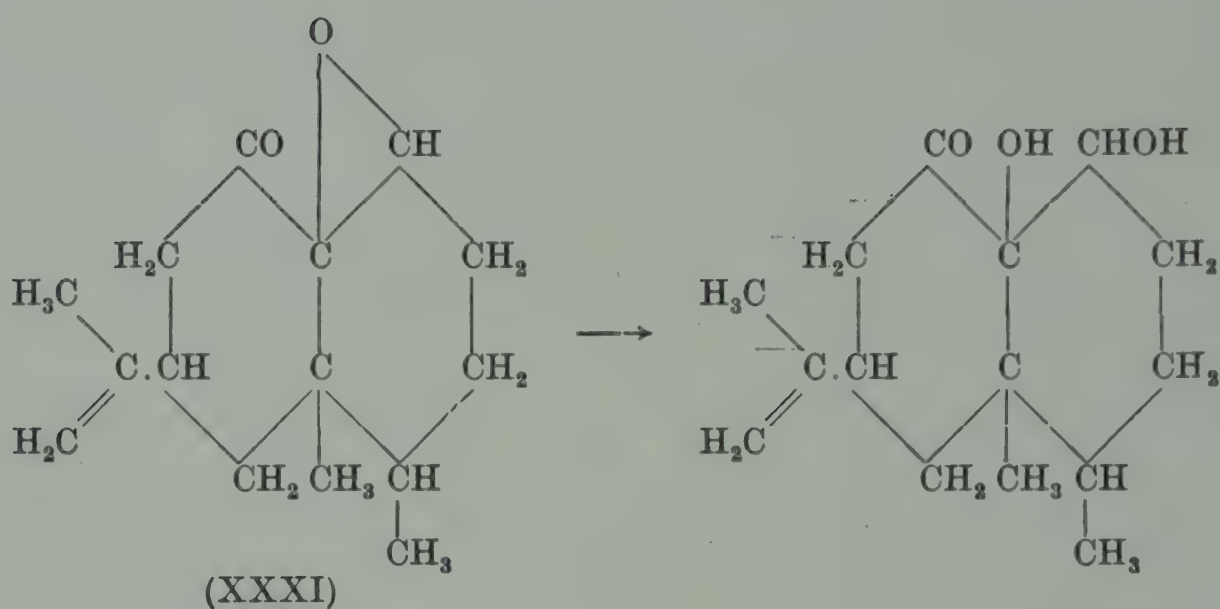
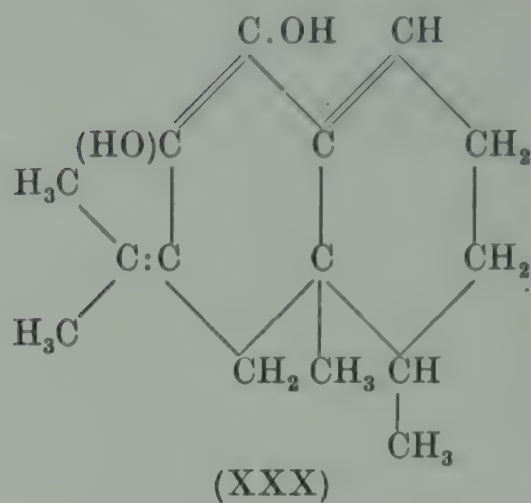


(XXI) suggested that hydroxyeremophilone was represented by (XXV), when the keto-acid from which the acid (XXI) was derived would be (XXVI). This assumption was, however, found to be incorrect. By the methylation with methyl sulphate of hydroxyeremophilone the *methyl ether*, b.p. $180^{\circ}/13$ mm., was prepared and catalytically hydrogenated to *tetrahydrohydroxyeremophilone methyl ether*, b.p. $168^{\circ}/16$ mm., $d_{19.8}^{19.8} 0.9983$, $n_D^{19.8} 1.4848$, $[\alpha]_{5461} +17.2^{\circ}$, 2:4-dinitrophenylhydrazone, m.p. 143° . Treatment of this ether with methyl magnesium iodide followed by selenium dehydrogenation gave 1:6-dimethyl-7-isopropyl-naphthalene (XXIX). From this it followed that hydroxyeremophilone must be (XXVII; $R=H$), the methyl ether being (XXVII; $R=CH_3$), when tetrahydrohydroxyeremophilone methyl ether would be (XXVIII). Whilst this formula (XXVII; $R=H$) evidently represents one of the tautomeric forms of the



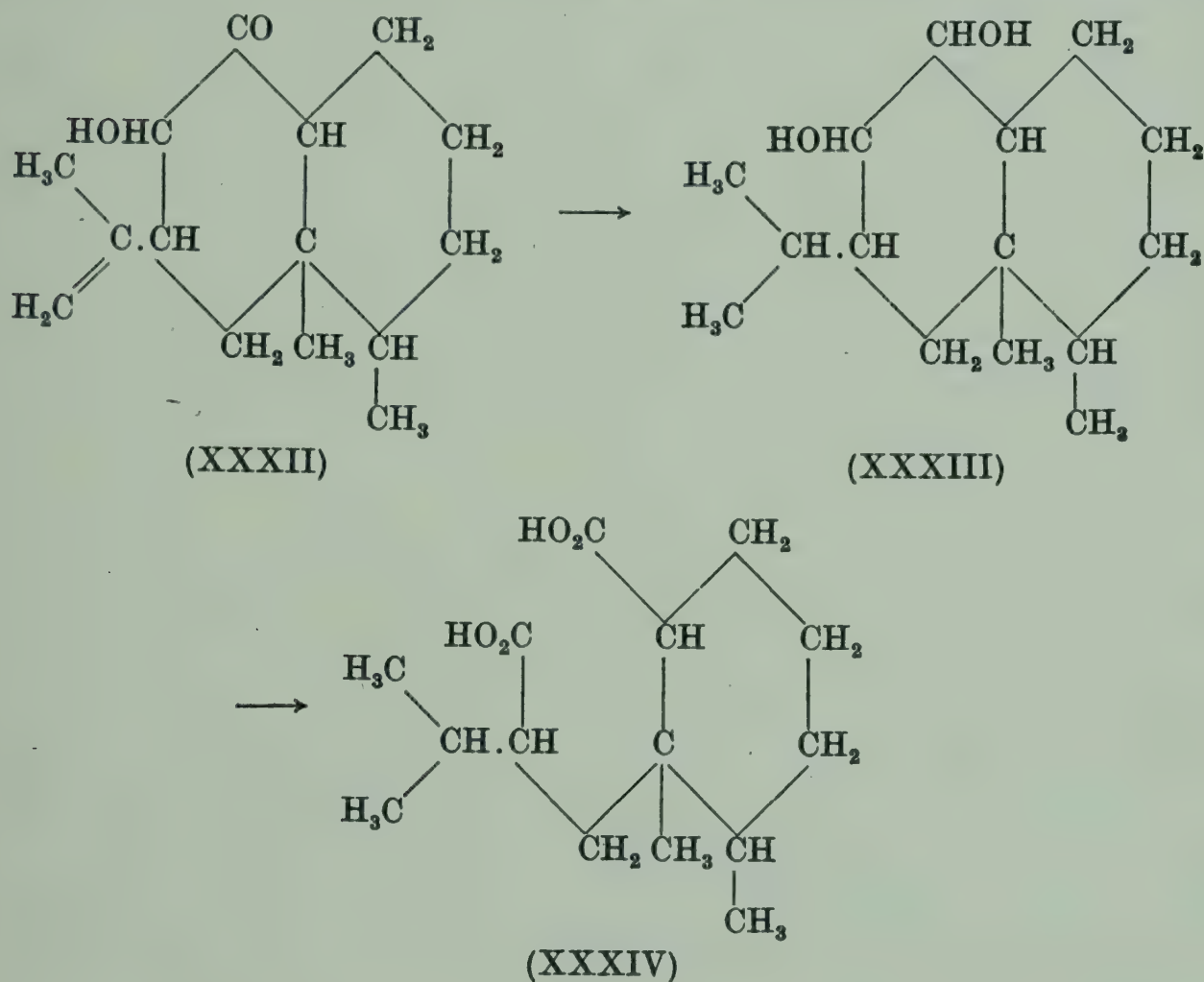
hydroxyketone, its bright yellow colour in the molten state suggests that it can exist also as the 1:2-diketone, although it has not proved possible to prepare any derivatives of this. A study of the absorption spectrum of the hydroxy-ketone and its benzoate suggests that in alcoholic solution the di-enolic form (XXX) is also present.

The assignment of structures (XIV) and (XXVII; $R=H$)



respectively to eremophilone and hydroxyeremophilone makes the formation of the latter from eremophilone oxide, which must be represented by (XXXI), somewhat difficult to explain. It was suggested by Gillam, Lynas-Gray, Penfold and Simonsen* that the mechanism of the reaction is in accordance with the scheme set out on p. 220, which involves a rearrangement.

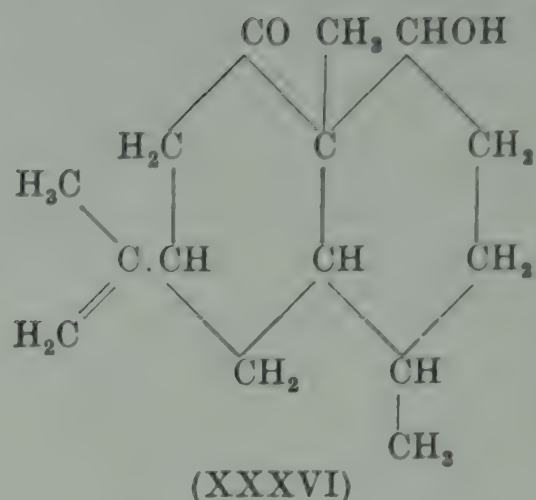
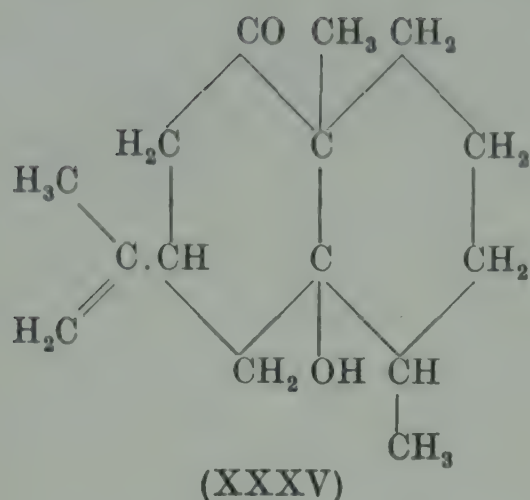
Hydroxydihydroeremophilone must now be represented by (XXXII), and confirmation of this structure was provided by the observation that both hydroxyeremophilone and hydroxydihydroeremophilone gave on reduction with sodium and alcohol a *glycol*, probably (XXXIII), since it gave on oxidation with lead tetra-acetate a *dibasic acid*, $C_{15}H_{26}O_4$, m.p. 193–194° (XXXIV).



Attention has already been directed (Vol. I, p. xi) to the fact that eremophilone and its congeners depart from the ordinary isoprene rule. Penfold and Simonsen† adopt a suggestion made by Sir Robert Robinson that it is possible that eremophilone is formed in nature by the dehydration of either (XXXV) or (XXXVI) by a molecular rearrangement.

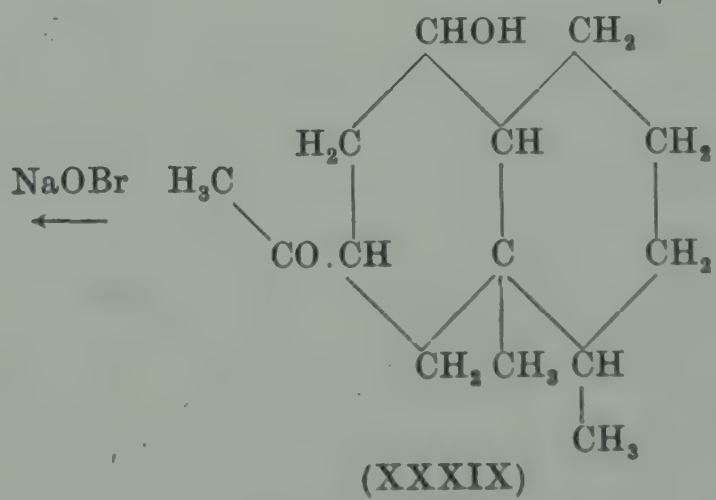
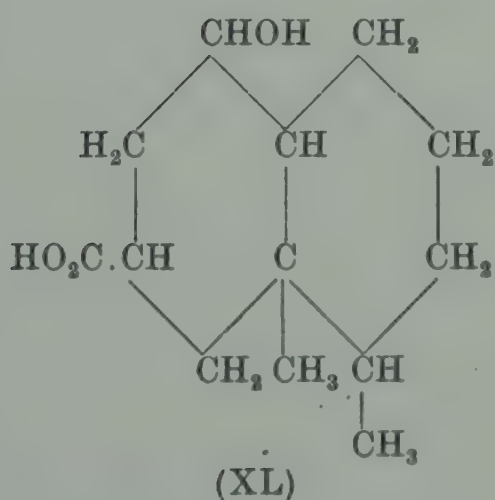
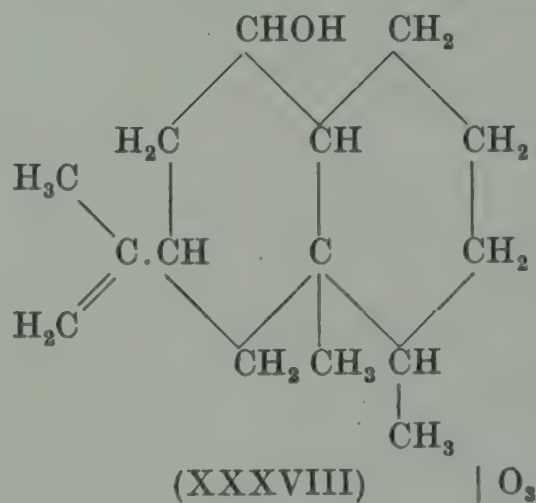
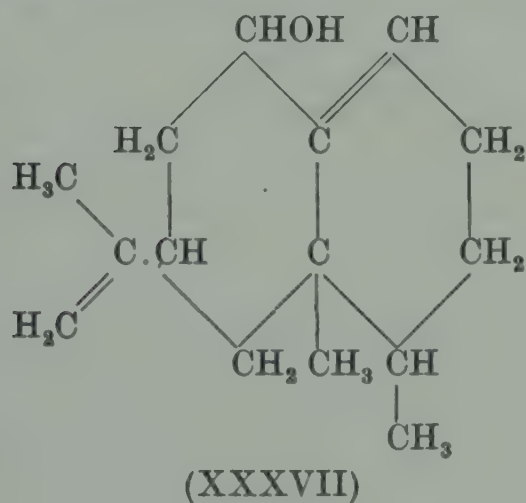
* *Loc. cit.*

† *Loc. cit.*



Although eremophilone did not react with the halogen acids, it gave a somewhat unstable *tetrabromide*, m.p. 116°, on bromination.

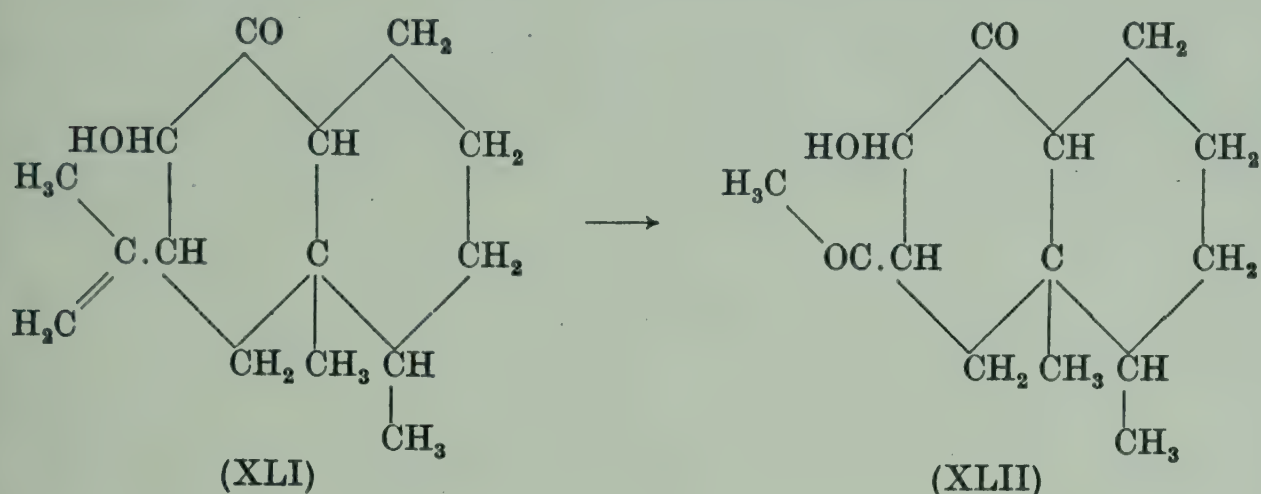
Reference was made above to the catalytic hydrogenation of eremophilone to tetrahydroeremophilone and also to its reduction by sodium and alcohol to dihydroeremophilol. When reduced with aluminium isopropoxide it gave *eremophilol* (XXXVII), b.p. 164–165°/13 mm., n_D^{25} 1.5202, $[\alpha]_{5461} -149.4^\circ$ (in ethyl acetate). Its absorption spectrum provided further proof that the two ethylenic linkages in the parent ketone were not conjugated. As was mentioned on p. 214, dihydroeremophilol



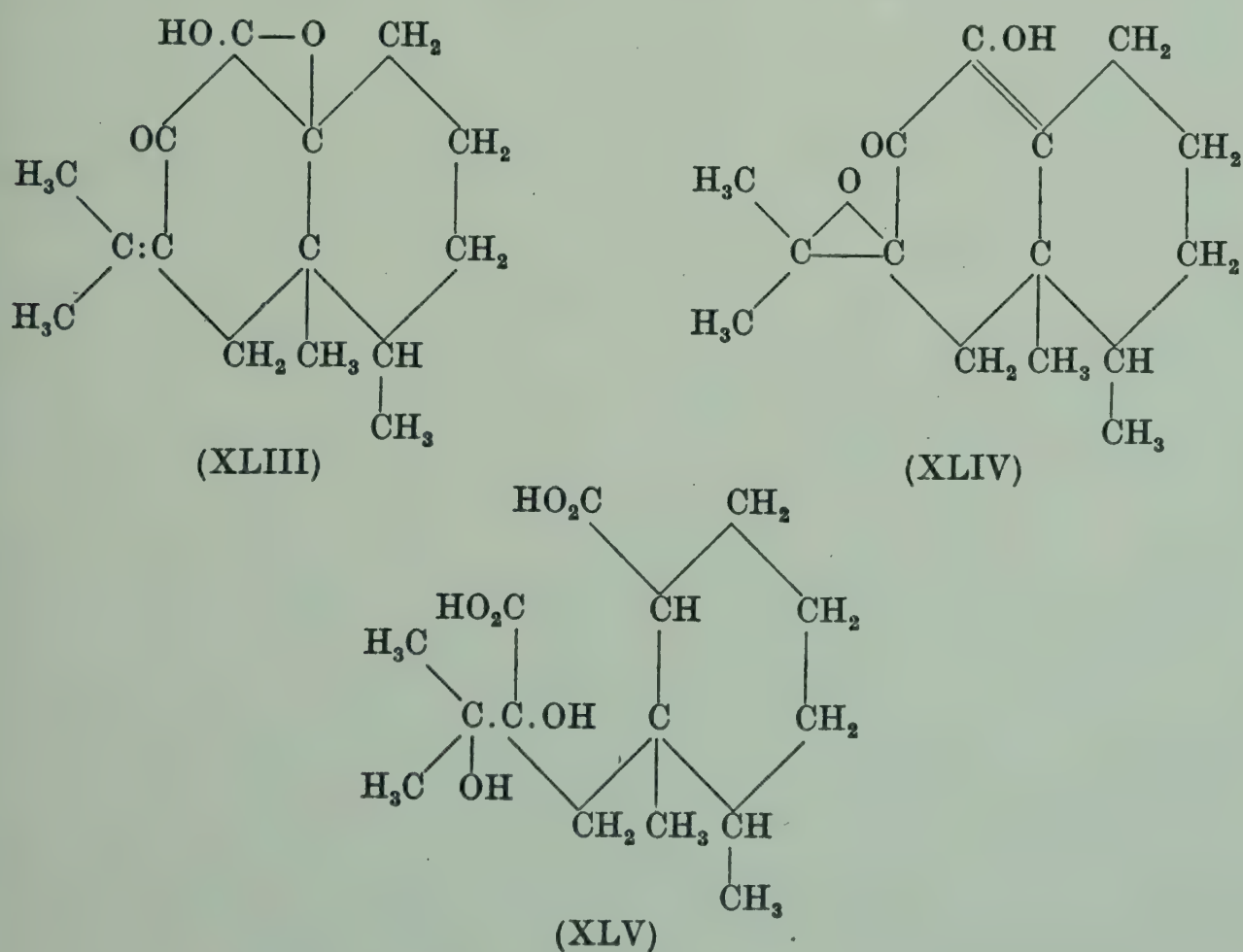
NaOBr

←

(XXXVIII) gave on ozonolysis formaldehyde and a keto-alcohol, which must now be represented by (XXXIX) and not by (VIII), whilst the hydroxy-acid must be (XL) and not (IX). A similar modification must be made in the formula (XI) assigned to the diketo-alcohol obtained by the ozonolysis of hydroxy-dihydroeremophilone (XLI); this must now be (XLII).

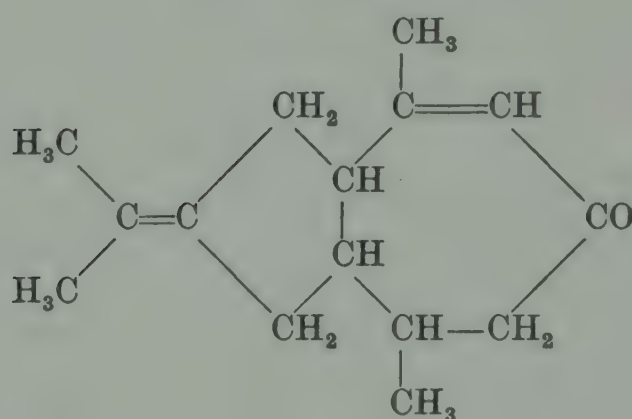


Finally, mention must be made of the products obtained by the oxidation of hydroxyeremophilone and hydroxydihydroeremophilone with hydrogen peroxide in alkaline solution. From the former an *oxide*, $C_{15}H_{22}O_3$, m.p. 150–151°, $[\alpha]_{5461} + 196^\circ$ (in methyl alcohol) and two *hydroxy-acids*, $C_{15}H_{26}O_6$, m.p. 167–168°



and 198° respectively, were obtained. The two acids were also formed from hydroxydihydroeremophilone. The structure of the oxide has not been determined but it is most probably either (XLIII) or (XLIV). There can be little doubt that the two acids are stereoisomeric modifications of (XLV). The two acids differ markedly in their reaction with acetyl chloride, the acid, m.p. $167-168^{\circ}$, yielding the *acetyl* derivative, m.p. $192-193^{\circ}$, of a lactonic acid, whilst the acid, m.p. 198° , gave a substance, m.p. 172° , which was insoluble in alkali, and which was either an *anhydride* or a *dilactone*.

VETIVONES



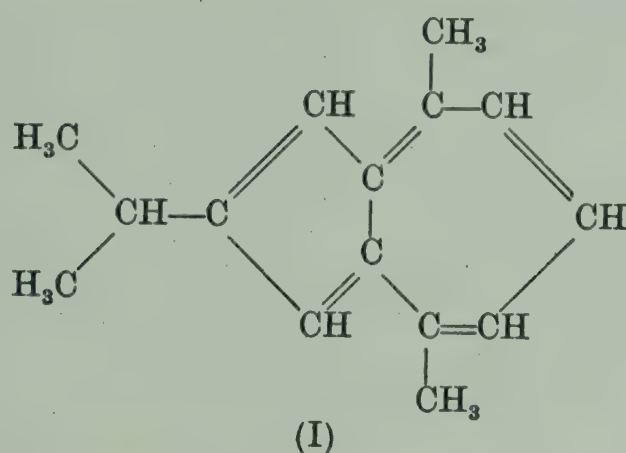
The essential oil of vetiver owes its importance in the perfumery industry to the presence of two interesting stereoisomeric bicyclic sesquiterpene ketones called α - and β -vetivones.* The two ketonic components of the oil were separated by the semicarbazone method and had the following constants: α -vetivone, b.p. $152-153^{\circ}/4$ mm., d^{20}_{20} 1.0074, n^{20}_D 1.5378, $[\alpha]^{20}_D + 225^{\circ}$ (in alcohol) and β -vetivone, b.p. $153-154^{\circ}/4$ mm., m.p. 44.5° , d^{20}_{20} 0.9991, d^{45}_{20} 0.9824, n^{20}_D 1.5378, $[\alpha]^{20}_D - 24.1^{\circ}$ (in alcohol). From the mother liquors of the semicarbazone fractionations a mixture of ketones, mainly the α - and β -vetivones, called "*isovetivones*" was obtained; a typical specimen had the constants b.p. $151-153^{\circ}/4$ mm., d^{20}_{20} 0.9955, n^{20}_D 1.5311, $[\alpha]^{20}_D + 138^{\circ}$ (in alcohol). The physical properties of these mixed "*isovetivones*" agree roughly with those of the so-called "*vetiverone*" of Sabetay and Trabaud† isolated from oil of vetiver with the aid of Girard's

* Pfau and Plattner, *Helv. Chim. Acta*, 1939, **22**, 640; compare Sabetay, *Bull. Soc. chim.* 1938 [v], **5**, 1422, Sabetay and Trabaud, *ibid.* 1939 [v], **6**, 740.

† Pfau and Plattner, *loc. cit.*

reagent. The molecular refraction data for the two vetivones (α -vetivone $[R_L]_D = 67.67$ and for β -vetivone $[R_L]_D = 67.80$) clearly indicated the presence of two rings and two double bonds, one of which was in conjugation with the ketone group ($C_{15}H_{22}O$; 2 ρ requires $[R_L]_D = 66.145$), and subsequent chemical evidence amply confirmed these indications.

The carbon skeleton of the vetivones was indicated by dehydrogenation experiments,* for in all cases a typical dehydrogenation product, vetivazulene (I) was isolated. The nature of

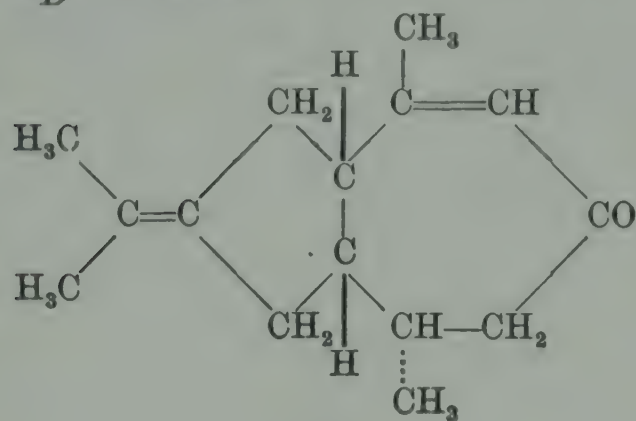


this hydrocarbon obviously implied the presence of mutually fused five- and seven-membered rings in the parent vetivones and detailed degradation experiments described below have fully supported this view. For convenience of exposition the chemistry of β -vetivone will be dealt with before that of the isomeric α -vetivone.

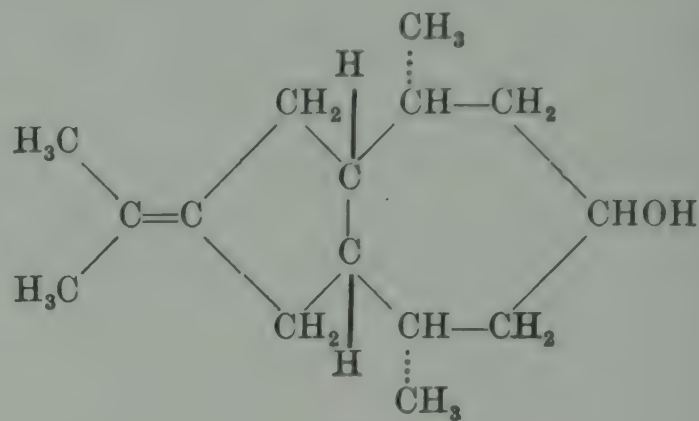
β -Vetivone (II) was easily reduced by catalytic hydrogenation (Raney nickel in alcohol) to the optically inactive *dihydro- β -vetivol* (III), m.p. 107° , or by sodium and alcohol to a mixture of dihydro- β -vetivols, (III) mixed with (IV), b.p. $130-150^\circ/2.5$ mm., $n_D^{20} 1.5151$. Reduction by the aluminium isopropoxide method gave principally β -vetivol (V), b.p. $129-130^\circ/0.5$ mm., $d^{20} 0.9956$, $n_D^{20} 1.5277$, together with a certain amount of a triply unsaturated *hydrocarbon*, probably (VI), b.p. $110^\circ/3.6$ mm., $d^{20} 0.9277$, $n_D^{20} 1.5225$, containing two of the ethylenic linkages in conjugation. Both the double bonds of β -vetivone were reduced by hydrogenation with a platinum catalyst in acetic acid, when the optically inactive *tetrahydro- β -vetivol* (VII), m.p. 76.5° , resulted. On oxidation with chromic acid, the tetrahydro- β -vetivol gave the also optically inactive *tetrahydro- β -*

* Pfau and Plattner, *Helv. Chim. Acta*, 1940, 23, 768.

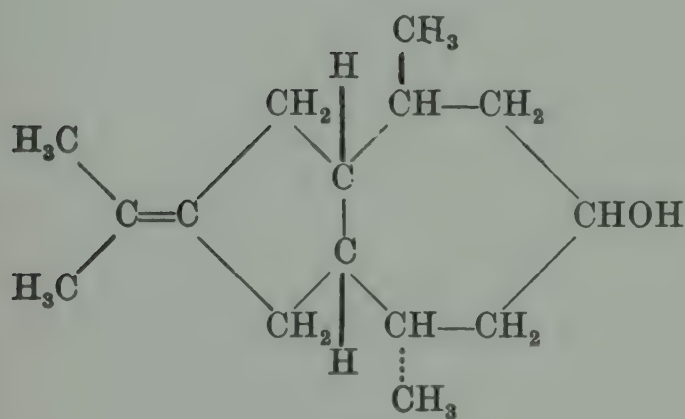
vetivone (VIII), m.p. 38° , n_D^{20} 1.4850. β -Vetivone was easily reduced by the Kishner procedure to a sesquiterpene hydrocarbon, β -vetivene (IX), b.p. $110\text{--}112^{\circ}/2.5\text{ mm.}$, d^{20} 0.9244, n_D^{20} 1.5116.



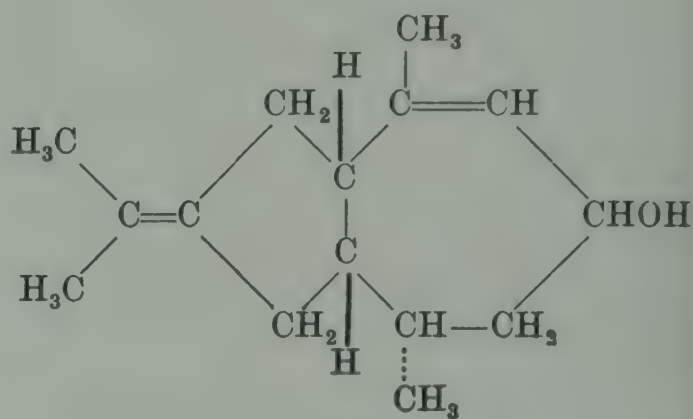
(II)



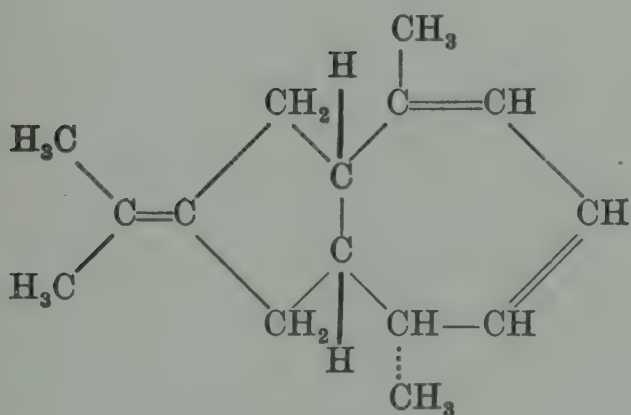
(III)



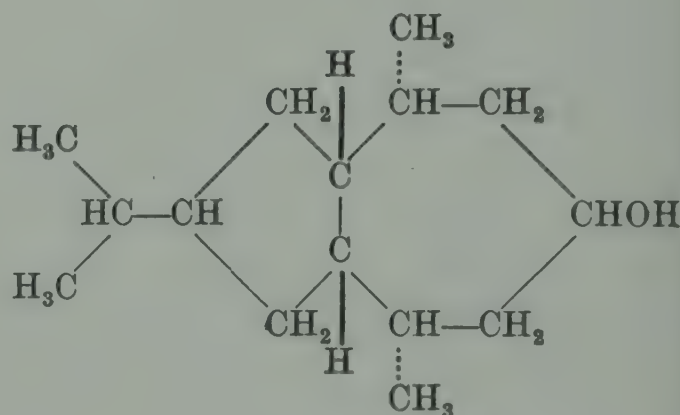
(IV)



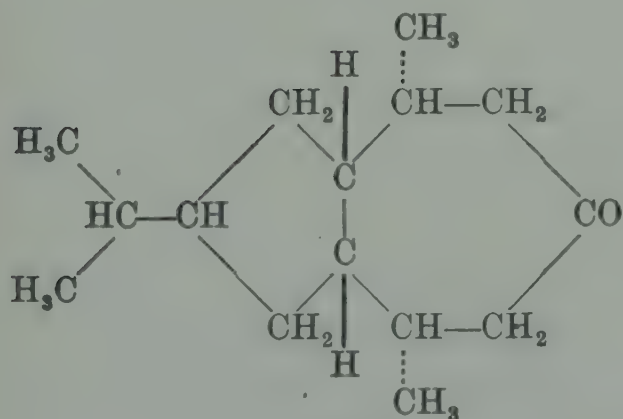
(V)



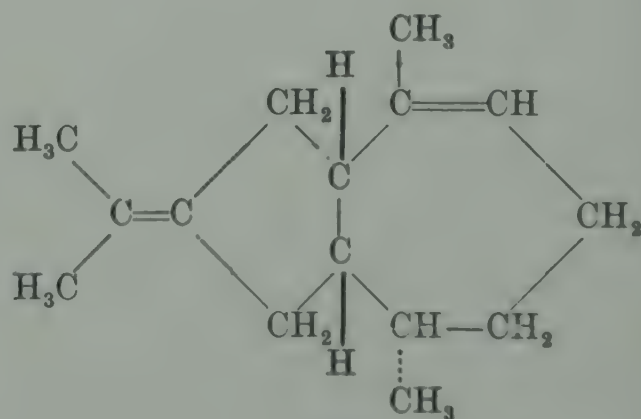
(VI)



(VII)

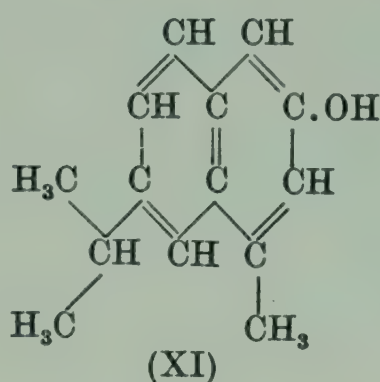
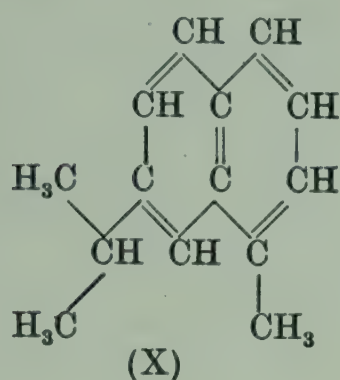


(VIII)

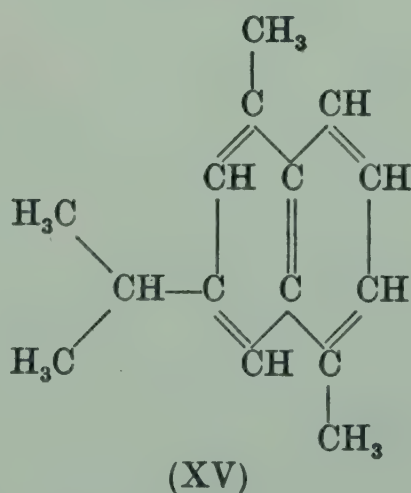
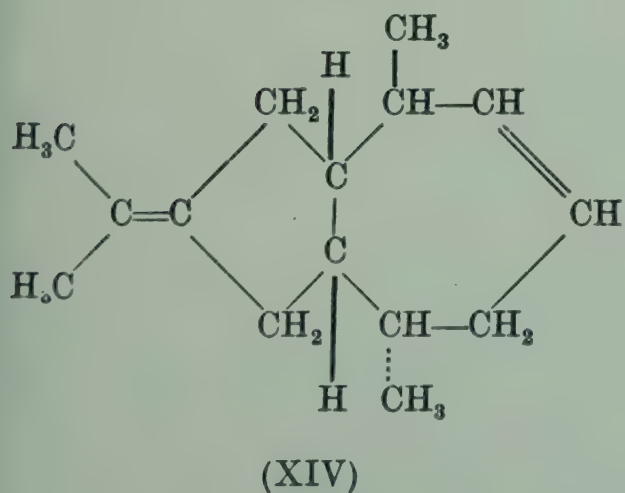
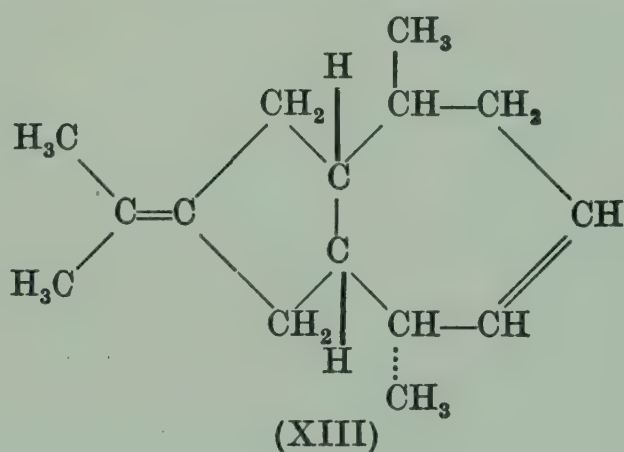
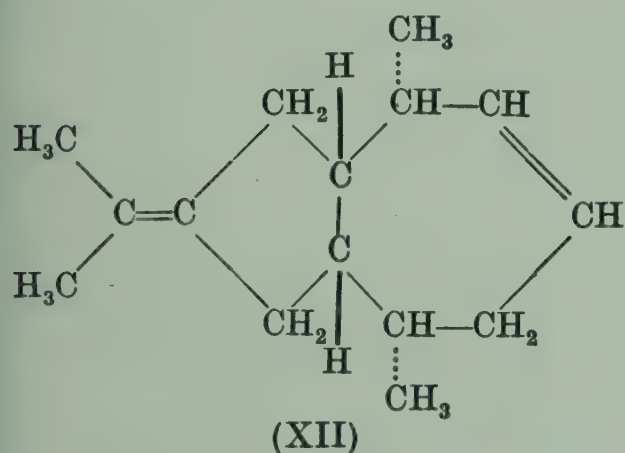


(IX)

Besides the characteristic dehydrogenation product vetivazulene (I) β -vetivone also gave, on treatment with palladised charcoal, a *naphthol*, $C_{14}H_{16}O$, m.p. 84° , *methyl ether*, m.p. 64° , which could be further degraded to *eudalene* (X). It was very probable that the naphthol should be represented by (XI). From the *isovetivones* it was possible to prepare, by the Kishner

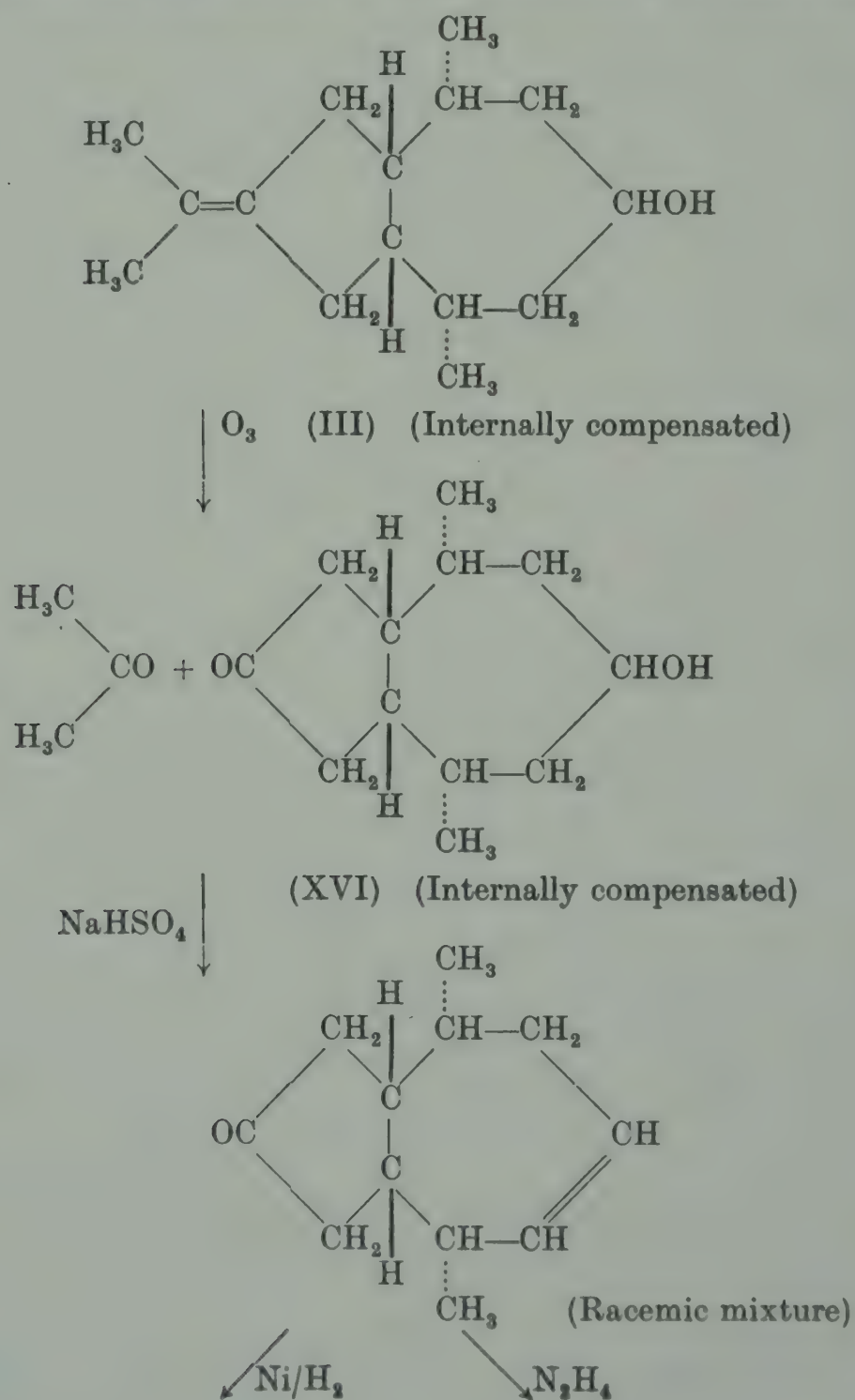


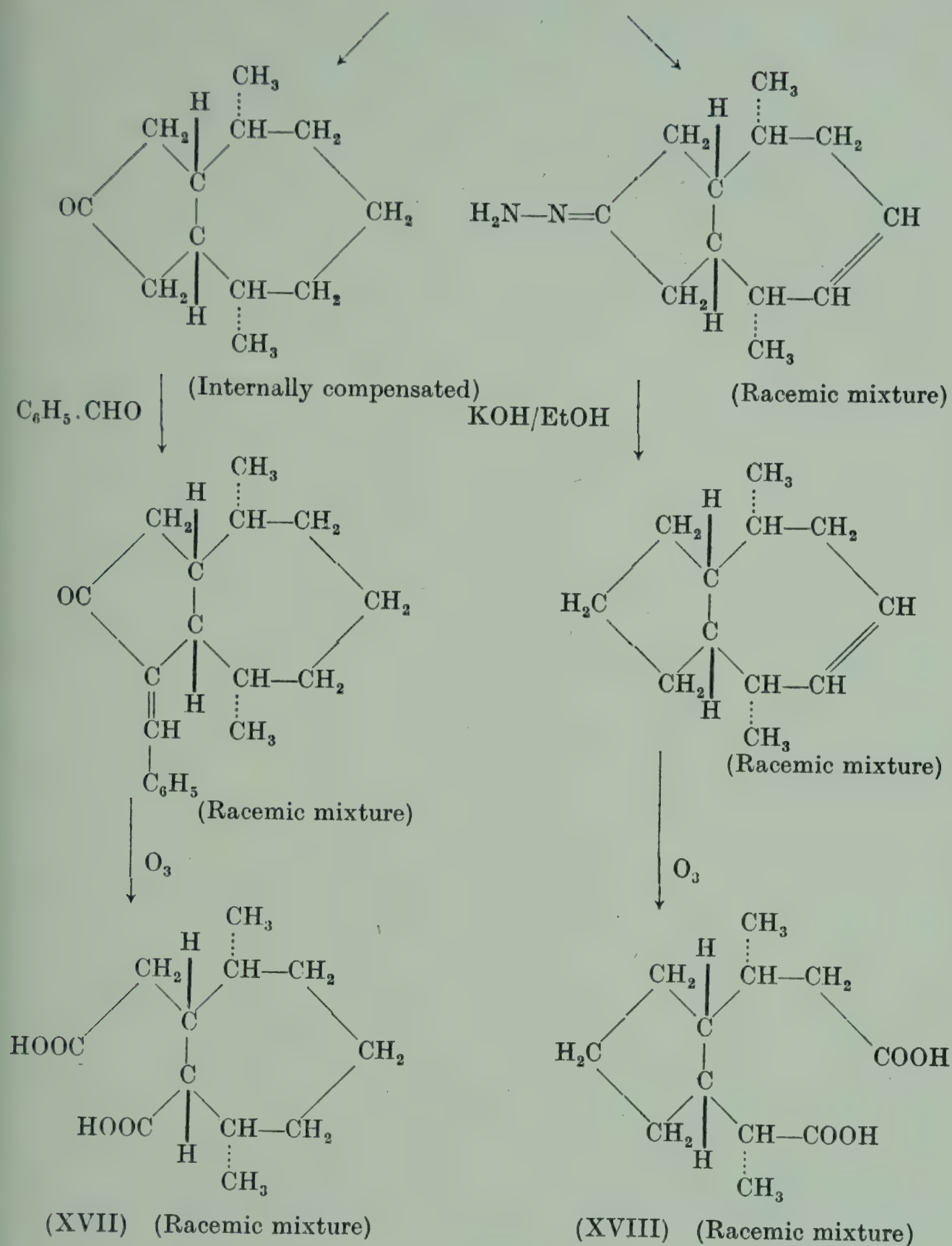
method, an *isovetivene* comparable with the β -vetivene mentioned above. This hydrocarbon, on dehydrogenation with sulphur or selenium, furnished vetivazulene and some eudalene. When dihydro- β -vetivol, (III) and (IV), prepared by the sodium and alcohol reduction of β -vetivone, was dehydrated by treatment with phosphorus tribromide followed by aniline, a mixture of hydrocarbons (XII), (XIII) and (XIV) resulted. This mixture



furnished vetivazulene and 1:5-dimethyl-7-isopropyl-naphthalene (XV) on dehydrogenation with sulphur. These experiments fully confirmed therefore the bicyclic nature of the vetivones.

More detailed evidence about the structure of β -vetivone was furnished by ozonolysis of the optically inactive dihydro- β -vetivol (III) and of β -vetivone itself. Both compounds gave acetone in high yield, thus showing the presence of an isopropylidene grouping. Furthermore it was possible to isolate a *hydroxy-ketone*, $C_{12}H_{20}O_2$ (XVI), as the second product of ozonolysis of the dihydro- β -vetivol. This hydroxy-ketone, m.p. 93° , was optically inactive as also was its *semicarbazone*, m.p. 199° . It was further degraded to two different racemic mixtures



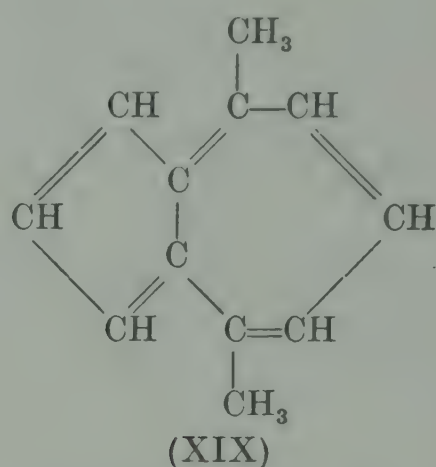


of dicarboxylic acids (XVII) and (XVIII), m.p.s $183-184^{\circ}$ and $168-169^{\circ}$ respectively, as indicated by the scheme given above.*

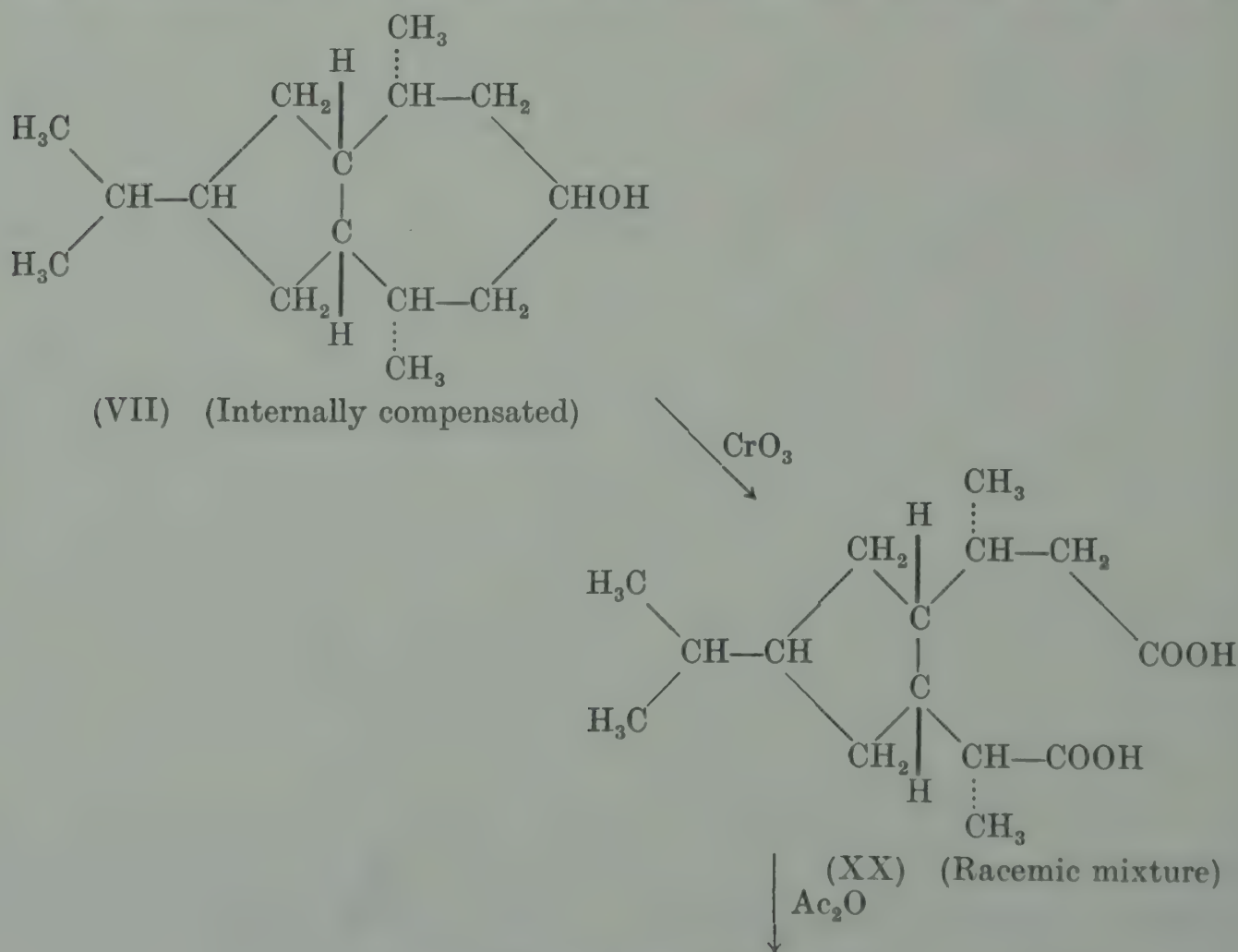
The optically active dihydro- β -vetivol (III) and (IV), obtained by sodium and alcohol reduction of β -vetivone gave in the same way an optically active hydroxy-ketone, $\text{C}_{12}\text{H}_{20}\text{O}_2$, on ozonolysis.

* Compare Bhattacharyya, *J. Ind. C.S.* 1945, 22, 214.

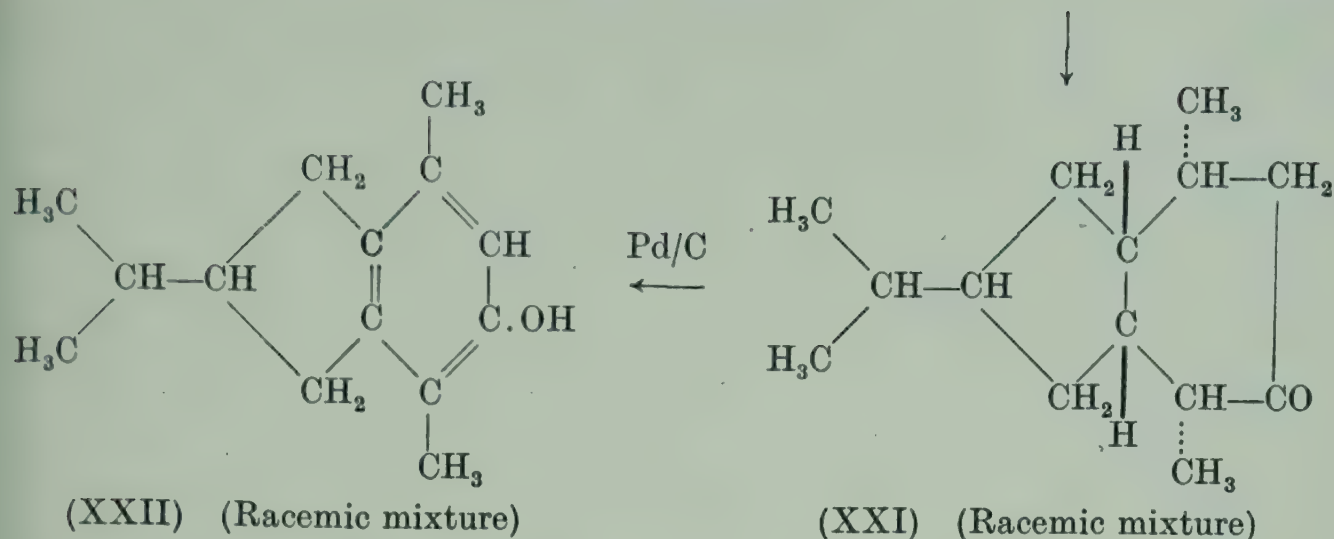
This ketone was dehydrated and the resultant unsaturated ketone was reduced to the corresponding alcohol; the alcohol in turn was dehydrated and the diethenoid hydrocarbon produced was dehydrogenated by treatment with selenium to 4:8-dimethylazulene (XIX), *picrate* m.p. 150°, which has been synthesised by Plattner and Wyss.*



When *tetrahydro-β-vetivol* (VII), or the corresponding ketone (VIII) (p. 226), was oxidised, most suitably with chromic acid, a racemic mixture of *dicarboxylic acids* (XX), m.p. 162·5–163·5, was produced. With acetic anhydride the mixed acids gave

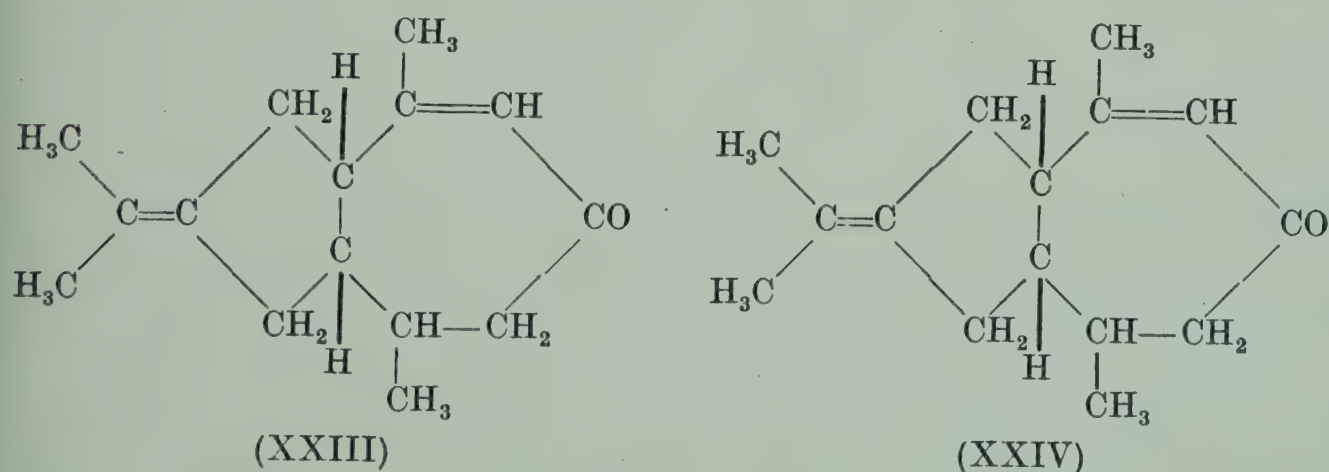


* *Helv. Chim. Acta*, 1941, **24**, 483.



2-isopropyl-4:7-dimethylhydrindan-5-one (XXI), semicarbazone m.p. 194–195°. Palladised charcoal dehydrogenation of this ketone furnished 2-isopropyl-4:7-dimethylindan-5-ol (XXII), m.p. 129–130°, identical with a synthetic specimen.

The many experimental facts summarised above lead to an unambiguous formula for β -vetivone. Since dihydro- β -vetivol (III) and so many of its derivatives are optically inactive, there must be a plane of symmetry in the molecule running through the isopropylidene and alcohol groups. This fact and the production of vetivazulene (I) and 4:8-dimethylazulene (XIX) by the dehydrogenation experiments as well as the various oxidative degradations already described show clearly that β -vetivone must have the formula (XXIII) with the hydrogen atom bridge-



head in the *cis*-relationship. The only remaining problem to be elucidated is the configuration of the methyl group and this will be discussed after a consideration of the α -vetivone formula.

α -Vetivone shows an extraordinary resemblance to β -vetivone in its chemical reactions and in most of its physical properties.*

* Naves and Perrottet, *Helv. Chim. Acta*, 1941, 24, 3.

Thus α -vetivone gave vetivazulene (I) and the naphthol $C_{14}H_{16}O$ (XI) on dehydrogenation by selenium. On ozonolysis acetone was produced in the same yield as with β -vetivone. By Kishner reduction of α -vetivone an α -vetivene, b.p. $124^{\circ}/4.2$ mm., $d_4^{20^{\circ}}$ 0.9244, $n_D^{20^{\circ}}$ 1.5171, $\alpha_D + 98.64^{\circ}$, resulted, with properties very similar to those for β -vetivene with the exception of the optical rotatory power. The rates of hydrogenation of the two vetivenes (platinum in acetic acid) were identical, as were the rates of hydrogenation of the two vetivones. From α -vetivone there was obtained, in this way, an optically inactive *tetrahydro- α -vetivol*, b.p. 132.5 – $134^{\circ}/2.5$ mm., $d_4^{20^{\circ}}$ 0.9758, $n_D^{20^{\circ}}$ 1.4962, oxidised by chromic acid to *tetrahydro- α -vetivone*. A comparative examination of the very similar Raman spectra of the α - and β -vetivones showed the presence in both compounds of roughly the same frequencies corresponding to $C=C$ and $C=O$ vibrations. Having regard to all these facts Naves and Perrottet* were forced to conclude that the α - and β -vetivones possessed the same formula (XXIII) and differed only in configuration at the asymmetric centre bearing the methyl group. It has not been possible to allot with certainty configurations to the vetivones, but consideration of many physical properties makes it seem likely that β -vetivone has the structure (II) and α -vetivone the structure (XXIV).

The α - and β -vetivones have been characterised by the formation of *semicarbazones* and *2:4-dinitrophenylhydrazones*. From α -vetivone the semicarbazone had m.p. 222 – 223° , $[\alpha]_D + 334.2^{\circ}$ (in acetic acid) and the 2:4-dinitrophenylhydrazone had m.p. 149° . From β -vetivone the constants were m.p. 228 – 229° , $[\alpha]_D - 71.1$ (in acetic acid) for the semicarbazone and m.p. 191° for the 2:4-dinitrophenylhydrazone. Both vetivones afforded vetivazulene, *picrate* m.p. 122° , *tosylate* m.p. 81° , *trinitrobenzoate* m.p. 151.5° , on treatment with dehydrogenating agents and they may be further characterised by reduction to the corresponding dihydro- and tetrahydro-vetivols mentioned above, and by the preparation of appropriate derivatives from these reduction products.

* *Loc. cit.*

C. KETONES OF UNKNOWN CONSTITUTION

ACORONE AND ISOACORONE

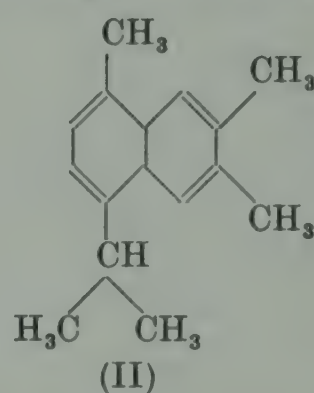
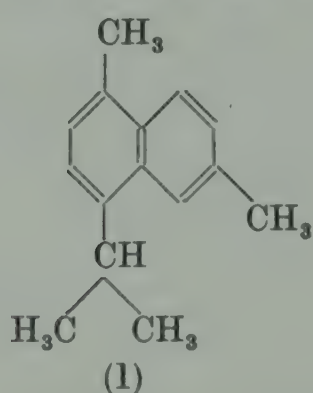
From the highest boiling fractions of the essential oil of *Acorus Calamus* L. Šorm and Herout* isolated the two sesquiterpene ketones *acorone*, $C_{15}H_{24}O_2$, m.p. 100–101°, $[\alpha]_D^{15^\circ} + 139.5^\circ$ (in alcohol), and *isoacorone*, $C_{15}H_{24}O_2$, m.p. 96–97°, $[\alpha]_D^{20^\circ} - 92.4^\circ$ (in alcohol). The chemistry of these ketones has been more extensively investigated by the same authors in a later paper.† *Acorone* and *isoacorone* are stereoisomeric diketones which are equilibrated in the presence of alkali. The equilibrium mixture contains about 65 per cent of the former compound. Since both ketones are saturated they must be bicyclic. The diketonic nature of *acorone* was proved by the formation of a *disemicarbazone*, m.p. 205–207° decomp., $[\alpha]_D^{17^\circ} + 437^\circ$ (in pyridine), by hydrogenation to the keto-alcohol, *acrolone*, $C_{15}H_{26}O_2$, *p*-nitrobenzoate, m.p. 133°, *semicarbazone*, amorphous, and by reduction by lithium aluminium hydride to *acordiol*, $C_{15}H_{28}O_2$, b.p. 130°/0.08 mm. Clemmensen reduction of *acorone* afforded a mixture of saturated and mono-unsaturated bicyclic hydrocarbons smoothly hydrogenated to the saturated *acorane*, b.p. 124–126°/13.5 mm., $d_4^{20^\circ} 0.8873$, $n_D^{20^\circ} 1.4817$, $[\alpha]_D^{20^\circ} + 33.0^\circ$ (in chloroform) and dehydrogenated to give *cadalene*, (I). *Acorane* and *cadalene* were obtained in exactly comparable ways from the diethylenic *hydrocarbon*, $C_{15}H_{24}$, b.p. 117–121°/11 mm., $d_4^{20^\circ} 0.9030$, $n_D^{20^\circ} 1.4960$, $[\alpha]_D^{20^\circ} + 39.4^\circ$ (in chloroform) prepared by dehydration of *acordiol* with phthalic anhydride.

The action of hot powdered caustic soda on *acorone* furnished a small amount of an $\alpha:\beta$ -unsaturated *ketone*, $C_{10}H_{16}O$, b.p. 99–103°/12 mm., $d_4^{20^\circ} 0.9337$, $n_D^{20^\circ} 1.4896$, $[\alpha]_D^{20^\circ} + 6.3^\circ$ (in ethanol), *semicarbazone*, m.p. 222–223°, *tetrahydro-derivative*, $C_{10}H_{20}O$, b.p. 89°/11 mm., $d_4^{20^\circ} 0.8878$, $n_D^{20^\circ} 1.4544$, and, as main product, an acid, $C_{15}H_{24}O_2$, *benzyl thiouronium salt*, m.p. 120.5°, *methyl ester*, b.p. 130°/2.2 mm., $d_4^{20^\circ} 0.9279$, $n_D^{20^\circ} 1.4740$, $[\alpha]_D^{20^\circ} \pm 0^\circ$. On catalytic hydrogenation the acid gave a saturated *tetrahydro-acid*, $C_{15}H_{28}O_2$, b.p. 150–152°/1 mm.

* *Coll. Czech. Chem. Comm.* 1948, **13**, 177.

† *Ibid.* 1949, **14**, 723.

Reaction of acorone with benzaldehyde afforded *mono-benzylideneacorone*, $C_{22}H_{28}O_2$, m.p. 185–186°, whilst treatment with methyl magnesium bromide furnished *methylacorolone*, $C_{16}H_{28}O_2$, m.p. 139°, reduced by lithium aluminium hydride to *methylacordioli*, $C_{16}H_{30}O_2$, m.p. 119°. Dehydration of the latter by heating with phthalic anhydride gave a *hydrocarbon*, $C_{16}H_{26}$, b.p. 131–133°/9 mm., $d_4^{20^\circ}$ 0.9082, $n_D^{20^\circ}$ 1.5015, dehydrogenated by palladised charcoal to a hydrocarbon regarded as 7-methylcadalene (II). Although this reaction sequence might be inter-



preted as indicating that acorone is a x:7-diketotetrahydrocadinene Šorm and Herout regard this as unlikely. Thus the infra-red spectrum of acorone is not similar to that of tetrahydrocadinene and the placing of the x-keto group at C_2 or C_3 would not explain its relative unreactivity. Position C_5 would be excluded as acorone is not a β -diketone.

isoAcorone gave only a *monosemicarbazone* m.p. 196–197°, decomp., $[\alpha]_D^{20^\circ} + 81.6^\circ$ (in pyridine), and on hydrogenation furnished *isoacorolone*, $C_{15}H_{26}O_2$, b.p. 146–150° (bath temp.)/0.2 mm. *isoAcorone* reacted with one equivalent of per-acid to give the lactone, *isoacoronolide*, $C_{15}H_{26}O_3$, m.p. 137°. In the same way acorone afforded the isomeric *acoronolide*, $C_{15}H_{26}O_3$, m.p. 188°. Acorone and *isoacorone* form a 2:1 molecular complex, m.p. 86°, which resists separation by crystallisation methods. It is, however, separable by chromatography.

Two further constituents of the essential oil of *Acorus Calamus* L. isolated by Šorm and Herout* were a ketone, *calamone*, $C_{15}H_{26}O$, b.p. 96–99°/0.44 mm., *semicarbazone*, m.p. 185–187°, $[\alpha]_D^{17^\circ} - 58.5^\circ$ (in pyridine) and an oxide, *acoroxide*, $C_{15}H_{24}O$, b.p. 135–137°/11.5 mm., d^{20° 0.9479, $n_D^{20^\circ}$ 1.4970, $[\alpha]_D^{20^\circ} + 12.1^\circ$ (in alcohol). The latter gave the saturated *tetrahydroacoroxide*, $C_{15}H_{28}O$, b.p. 134–136°/10 mm., d^{20° 0.9130, $n_D^{20^\circ}$ 1.4745, $[\alpha]_D^{20^\circ}$

* *Loc. cit.*

+ 2.4° (in alcohol), on catalytic hydrogenation and it must, therefore, contain one carbon ring and one oxide ring. Dehydrogenation of a crude acoroxide fraction afforded cadalene.

ISHWARONE

The ketone, *ishwarone*, $C_{15}H_{22}O$, occurs in the essential oil present in the roots of *Aristolochia indica*.^{*} The ketone, b.p. 118–120°/1 mm., d_{30}^{30} 1.029, n_D^{30} 1.5122, α_D^{30} –46.5°, has been characterised by the preparation of an *oxime*, m.p. 133°, a *semicarbazone*, m.p. 240°, a *p-nitrophenylhydrazone*, m.p. 186.5°, and a *2:4-dinitrophenylhydrazone*, m.p. 167.5°. No evidence of its structure has been recorded.

According to the same authors the oil contains also a hydrocarbon, *ishwarene*, $C_{15}H_{24}$, b.p. 130–132°/10 mm., d_{30}^{30} 0.9227, n_D^{30} 1.5035, α_D^{30} –42.4° and an alcohol, *ishwarol*, $C_{15}H_{24}O$, b.p. 126–128°/1 mm., d_{30}^{30} 0.9926, n_D^{30} 1.5095, α_D^{30} –7.3°. No crystalline derivatives of either of these substances have been prepared and their homogeneity would appear to be doubtful.

ZIERONE

The ketone, *zierone*, $C_{15}H_{22}O$, occurs in the essential oil from *Zieria macrophylla*.[†] The structure of the ketone has not been determined, but it is probably a tricyclic ketone containing one ethylenic linkage which is not in the $\alpha:\beta$ -position to the carbonyl group.

Zierone is a viscid colourless oil, b.p. 147–149°/18 mm., d_{15}^{15} 0.9752, n_D^{20} 1.514, $[\alpha]_D$ –145.8°, but it has not been obtained pure. It can be characterised by the preparation of the *semicarbazone*, m.p. 182° and the *2:4-dinitrophenylhydrazone*, m.p. 95–97°. Its hydroxymethylene derivative is an oil giving an intense purple coloration with alcoholic ferric chloride and yielding a *2:4-dinitrophenylhydrazone*, m.p. 155–157°.

On reduction with sodium and alcohol the unsaturated alcohol, *zierol*, b.p. 151–152°/17 mm., n_D^{20} 1.5094, $[\alpha]_{5461}$ +37.4° (in methyl alcohol) was obtained from which by oxidation with chromic acid the parent ketone can be regenerated.

^{*} Rao, Majunath and Menon, *J. Ind. C.S.* 1934, **12**, 496.

[†] Penfold, *J. Proc. Roy. Soc. New South Wales*, 1926, **60**, 104; Bradfield, Penfold and Simonsen, *ibid.* 1933, **67**, 200.

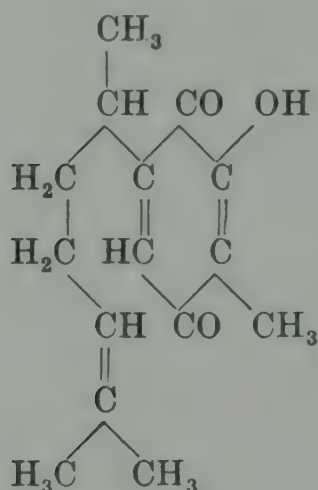
Zierone was very resistant to the action of oxidising agents and no degradation products have been characterised.

Dehydrogenation with selenium of the hydrocarbon, prepared from zierol by dehydration with formic acid, gave in poor yield an azulene, resembling Se-guaiazulene, *picrate*, m.p. 110–111°.*

D. HYDROXY DIKETONE

PEREZONE

[*Pipatzahoic acid*, 6-hydroxy-5-methyl-2-(1:5-dimethyl- Δ^4 -hexenyl) 1:4-benzoquinone]



Perezone is the only example of a sesquiterpene quinone so far discovered. It was first isolated by Weld[†] from the roots of *Trixis pipitzahuac* Schaffner in the form of golden yellow plates, m.p. 103–104°. Perezone was readily reduced, taking up two hydrogen atoms, to give a *leuco* compound, which was easily reoxidised to perezone on standing in the air. One of the oxygen atoms was present as an acidic hydroxyl, since perezone formed metallic salts. With aniline, perezone reacted to give a mono-anilino derivative, hydrolysable by sulphuric acid to a *hydroxy-perezone* containing two acidic hydroxyls. With bromine, perezone reacted to form an unstable dibromide. These facts, established in the course of extensive investigations by Mylius,[‡] Anschütz,[§] Sanders^{||} and Remfrey,[¶] clearly showed that perezone was a monohydroxy-1:4-quinone and suggested the presence of alkyl and alkenyl side chains attached to the quinonoid nucleus.

* Compare Ruzicka and Haagen-Smit, *Helv. Chim. Acta*, 1931, **14**, 1004.

† *Annalen*, 1855, **95**, 188.

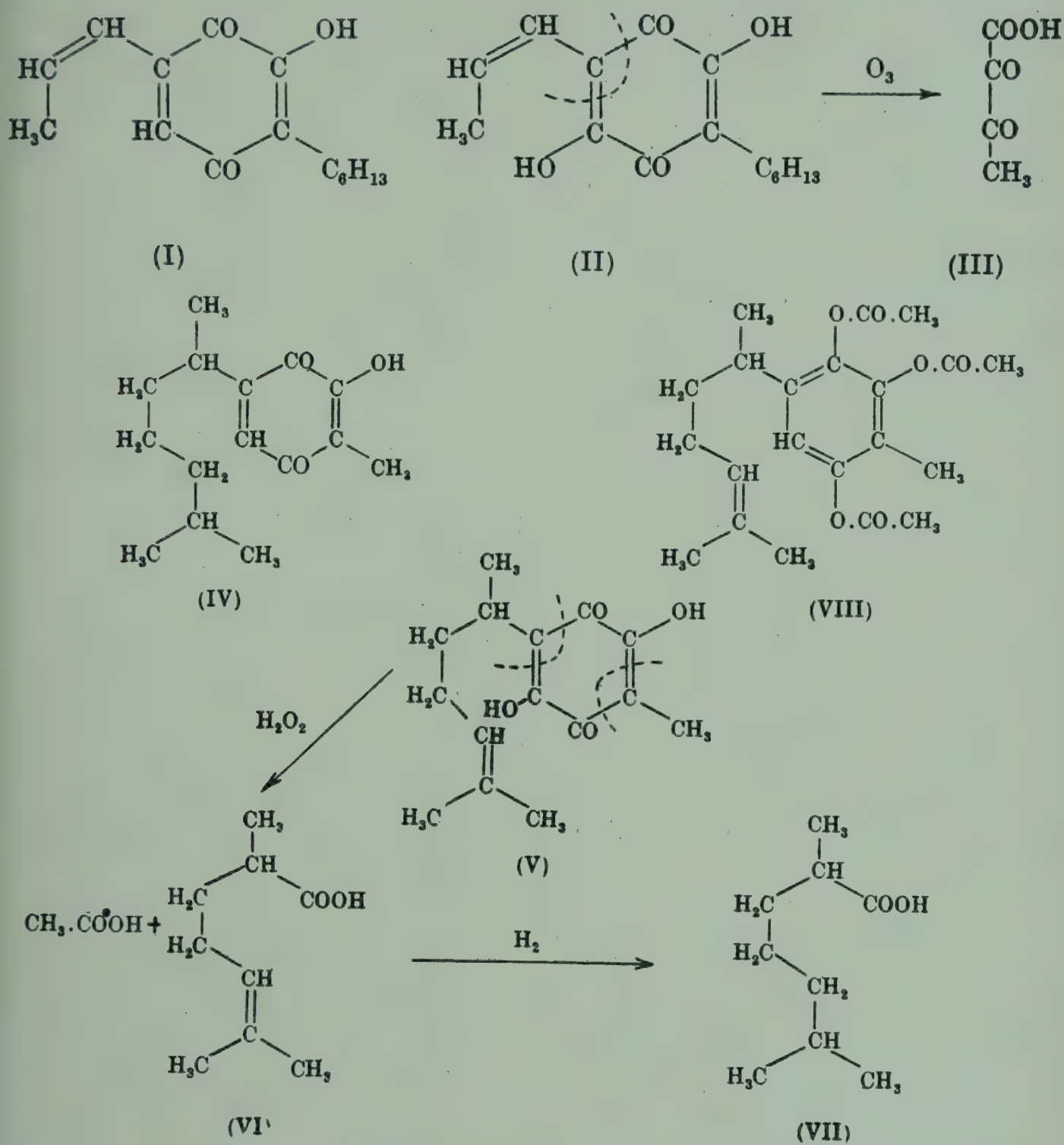
‡ *Ber.* 1885, **18**, 480, 936.

§ *Ibid.* pp. 709, 715; *Annalen*, 1887, **237**, 90.

|| *Proc. C.S.* 1906, **22**, 134.

¶ *J.C.S.* 1913, **103**, 1076.

Fichter, Jetzer and Leepin* confirmed the validity of these conclusions and suggested the formula (I) for perezone, on the basis of the isolation of 2:3-diketobutyric acid (III) by ozonolysis of the closely related hydroxyperezone.† Although, as Remfrey



pointed out, the 2:3-diketobutyric acid might equally well have arisen from the presence of a methyl side chain, the correct formula for perezone was not established until 1935. In this year Kögl and Boer‡ finally characterised the side chains of perezone by oxidative degradation. The presence of a double bond in one

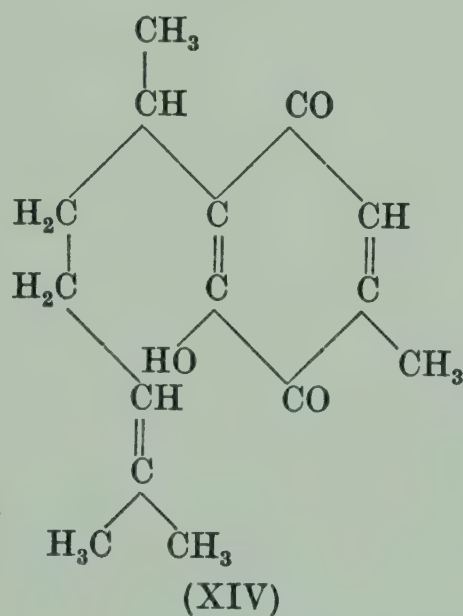
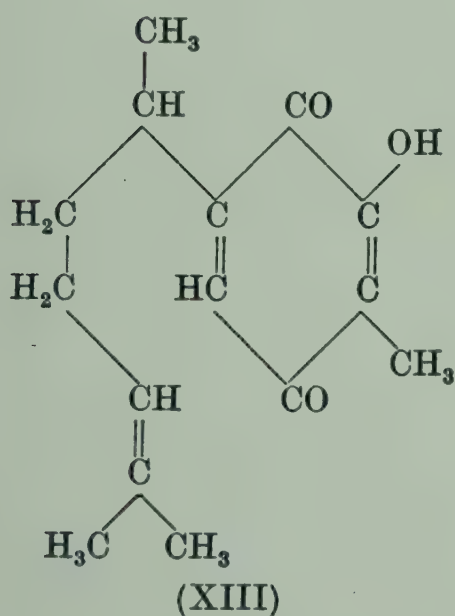
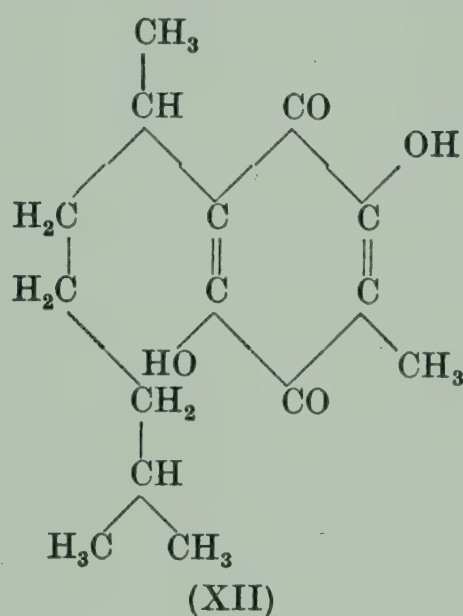
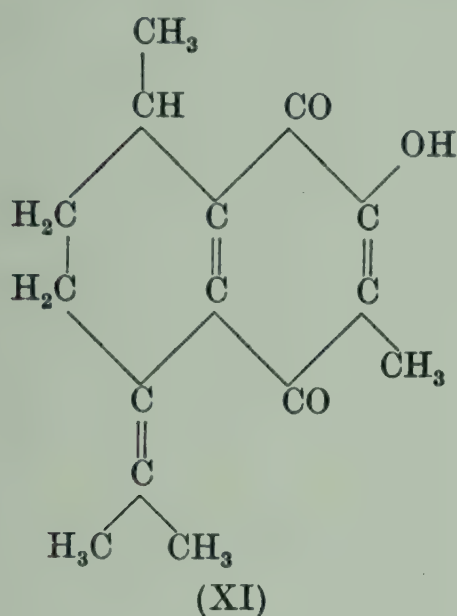
* *Annalen*, 1913, 395, 15.

† (II) according to Fichter, Jetzer and Leepin.

‡ *Rec. trav. chim.* 1935, 54, 779.

and by conversion, *via* hydroxyperezone (V), to perezinone (XI) m.p. 143–145°.

The dry distillation of perezone at atmospheric pressure causes isomerisation to a saturated substance $C_{15}H_{20}O_3$ called *pipitzol*, m.p. 141°, $[\alpha]_D + 14.4^\circ$ (in chloroform), $+ 9.0^\circ$ (in alcohol). One of the oxygen atoms in this compound is present as an acetylatable hydroxyl and the resulting *monoacetate*, m.p. 115°, $[\alpha]_D + 6.2^\circ$ (in chloroform), can also be prepared by the acetylation

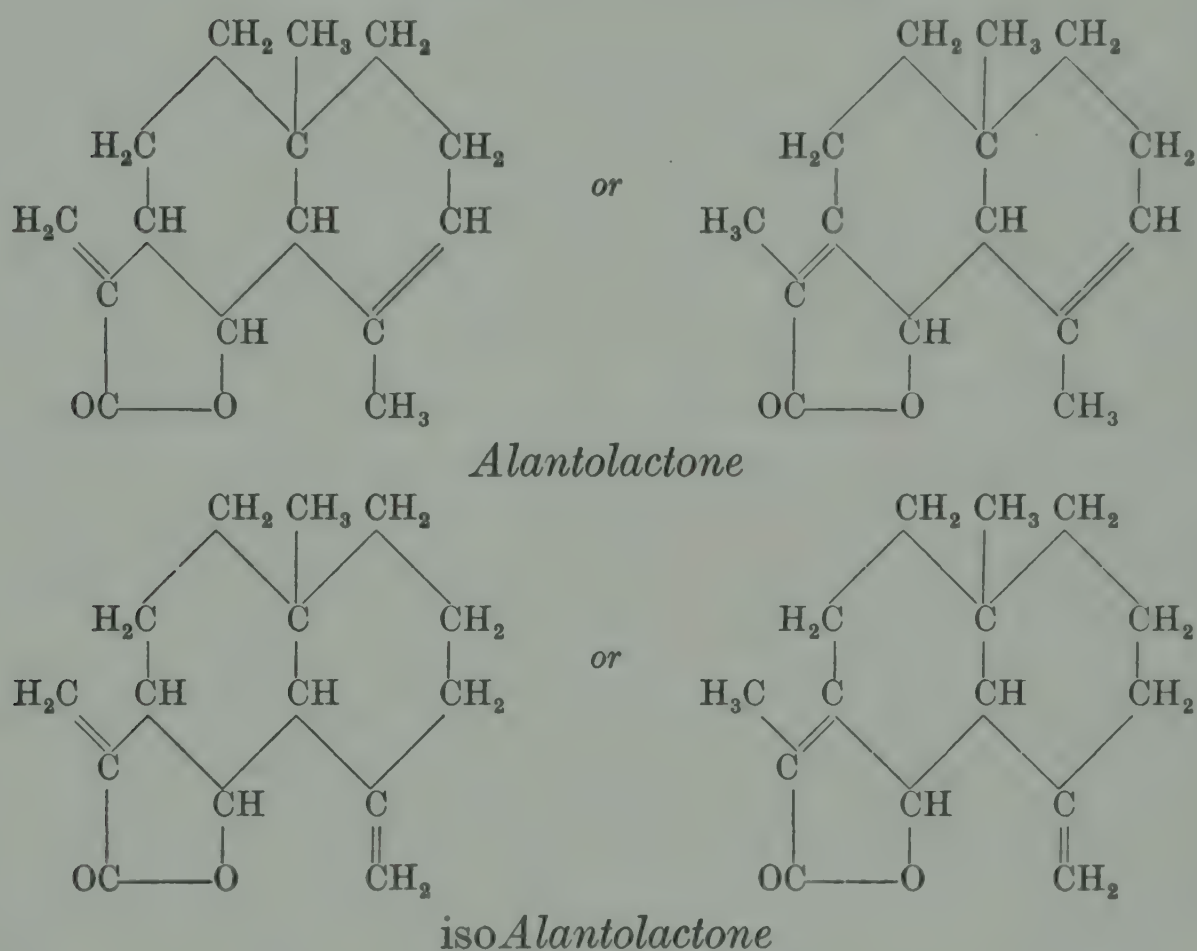


of perezone itself under drastic conditions. The other two oxygen atoms have not been characterised and no structure has as yet been suggested for this peculiar compound. Indeed the experimental data recorded in the literature cannot be reconciled with each other or with the structure established for perezone.

CHAPTER V
LACTONES, KETO-LACTONES AND
HYDROXY KETO-LACTONES

A. LACTONES

THE ALANTOLACTONES



The roots of *Inula Helenium* have been known for many years to contain two bitter principles to which the names *alantolactone* and *isoalantolactone* have been given. Alantolactone, $C_{15}H_{20}O_2$, m.p. 76° , b.p. $192^\circ/10$ mm., was first investigated by Gerhardt* and later by Kallen.† The presence of the isomeric *isoalantolactone*, m.p. 115° , was also first recognised by Kallen.‡ A third bitter principle, *dihydroisoalantolactone*, $C_{15}H_{22}O_2$, m.p. 174° , $[\alpha]_D^{22} + 72.0^\circ$ (in alcohol) has been isolated from the same source in more recent years by Hansen.§

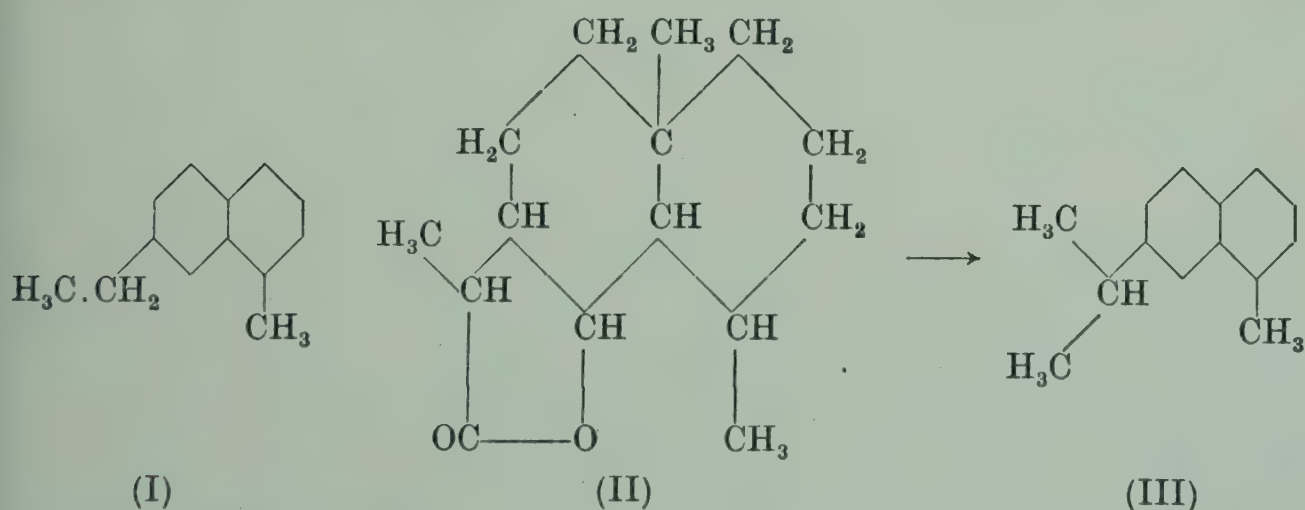
* *Annalen*, 1840, **34**, 192.

† *Ber.* 1876, **9**, 154.

‡ *Ber.* 1873, **6**, 1507. Alantolactone and *isoalantolactone* have also been known as helinin and *isohelinin*, but the former names are now generally accepted.

§ *Ber.* 1931, **64**, 67; compare Ruzicka and Pieth, *Helv. Chim. Acta*, 1931, **14**, 1090.

The earlier investigations of Bredt and Posth* and of Sprinz† had established the lactonic nature of both alantolactone and isoalantolactone. Thus with alkali it was shown that alantolactone was converted to *alantolic acid*, $C_{15}H_{22}O_3$, m.p. 94° ,‡ *methyl ester*, m.p. 83° , *ethyl ester*, m.p. $79-80^\circ$, *amide*, m.p. *ca.* 210° decomp. (*acetyl derivative*, m.p. 179° decomp.), and isoalantolactone to *isoalantolic acid*, $C_{15}H_{22}O_3$, m.p. 143° , *amide*, m.p. $237-239^\circ$ (*acetyl derivative*, m.p. 212°), both of which acids readily reverted to the parent lactones on heating. Bredt and Posth had also obtained some insight into the carbon skeleton of alantolactone, observing that on zinc dust distillation it gave a mixture of naphthalene, propylene and other products. Furthermore Bredt and Posth obtained by distillation of alantolactone with phosphorus pentoxide two *hydrocarbons*, $C_{12}H_{16}$, b.p. $132^\circ/10$ mm., and $C_{13}H_{16}$, b.p. $152^\circ/10$ mm., both of which afforded naphthalene on zinc dust distillation. The presence of a potentially naphthalenic skeleton indicated by these experiments was confirmed by Hansen§ and by Ruzicka and Melsen,|| who showed that on dehydrogenation with selenium alantolactone, isoalantolactone and dihydroisoalantolactone all furnished 1-methyl-7-ethylnaphthalene (I), obtainable in a somewhat analogous manner from artemisin (see p. 312). Both alantolactone and isoalantolactone gave, on catalytic hydrogenation, the same saturated stereoisomer of deoxytetrahydrosantonin (see p. 259), *tetrahydroalantolactone*, $C_{15}H_{24}O_2$ (II), m.p. 147.5° , $[\alpha]_D +15.5^\circ$ (in alcohol). The *methyl ester*, m.p. 114° , of the corresponding



* *Annalen*, 1895, **285**, 356.

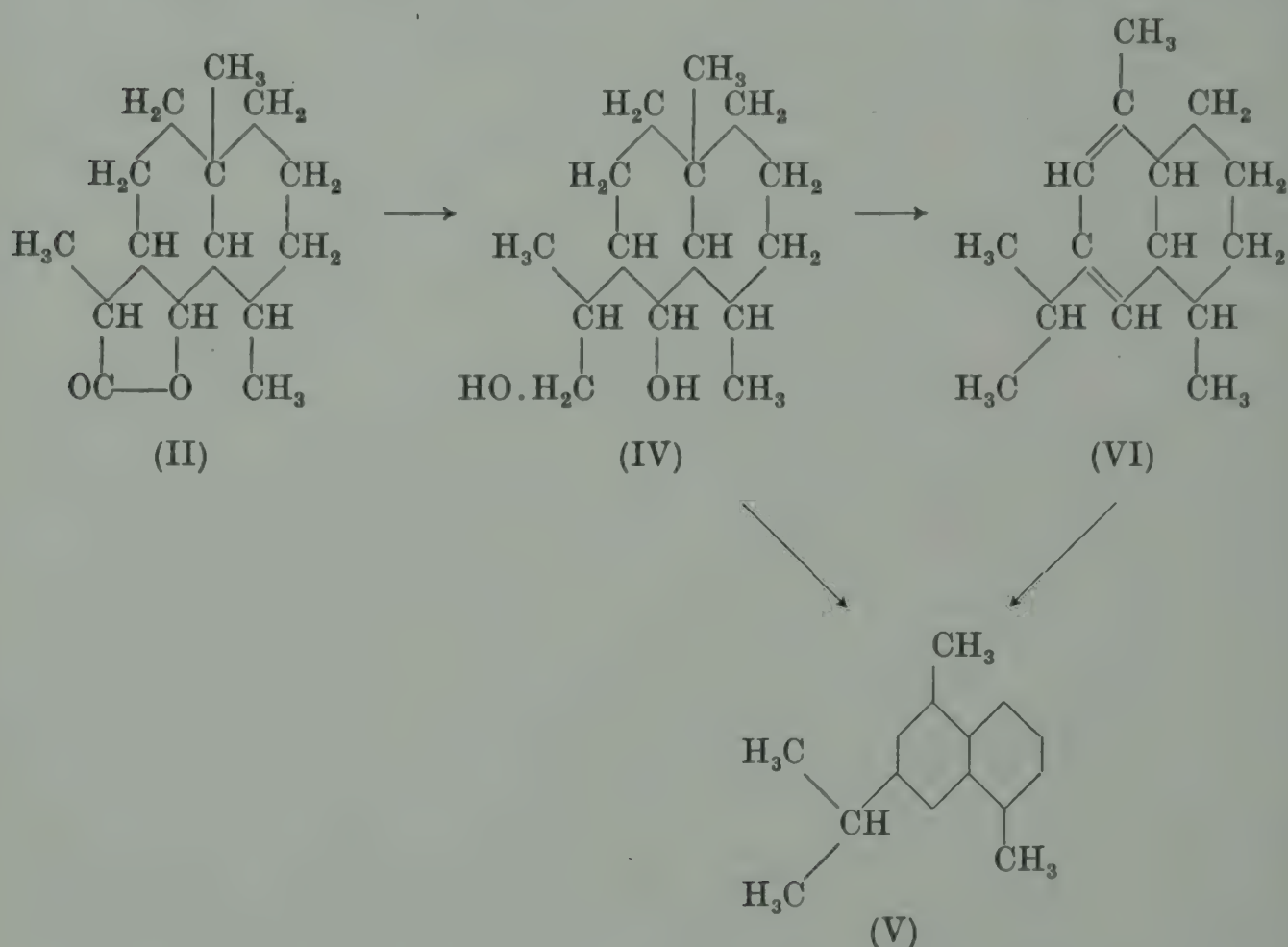
† *Ber.* 1901, **34**, 775; *Arch. Pharm.* 1901, **239**, 201.

‡ Hansen, *Ber.* 1931, **64**, 943, records m.p. $135-136^\circ$.

§ *Ber.* 1931, **64**, 67.

|| *Helv. Chim. Acta*, 1931, **14**, 397.

acid, on reduction by sodium and alcohol and treatment of the product with red phosphorus and hydriodic acid followed by dehydrogenation with selenium, afforded eudalene (III).^{*} Ruzicka and Melsen[†] and Ruzicka and Pieth[‡] have provided conclusive evidence that alantolactone and isoalantolactone belong to the eudalene group of sesquiterpenes. By reduction with sodium and alcohol tetrahydroalantolactone furnished the corresponding *glycol*, $C_{15}H_{28}O_2$ (IV), b.p. 167–170°/0.4 mm., which after treatment with hydrobromic acid and quinoline gave a doubly unsaturated *hydrocarbon*, $C_{15}H_{24}$, b.p. 130–133°/12 mm., $d_4^{19^\circ}$ 0.918, $n_D^{19^\circ}$ 1.5104. By selenium dehydrogenation of this hydrocarbon 1:5-dimethyl-7-isopropyl-naphthalene (V), *picrate*, m.p. 114° was obtained, the identity of which has been proved by synthesis.[§] In an attempt to repeat the experiments of



* Hansen, *Ber.* 1931, **64**, 943; compare, however, Ruzicka and Pieth, *Helv. Chim. Acta*, 1931, **14**, 1090.

† *Loc. cit.*

‡ *Loc. cit.*

§ Ruzicka, Pieth, Reichstein and Ehmann, *Helv. Chim. Acta*, 1933, **16**, 268; it was originally reported by Ruzicka and Melsen (*ibid.* 1931, **14**, 397) that this on dehydrogenation gave a hydrocarbon, 1-methyl-7-isopropenyl-naphthalene, *picrate*, m.p. 87–88°, but Ruzicka and Pieth (*ibid.* 1931, **14**, 1090) were unable to repeat this observation and obtained, instead, the hydrocarbon (V), described in the text.

Hansen referred to above Ruzicka and Pieth reduced the glycol (IV), with red phosphorus and hydriodic acid and dehydrogenated the product with selenium, when they also obtained 1:5-dimethyl-7-isopropylnaphthalene (V). This hydrocarbon must be formed by a peculiar and unexpected rearrangement and its precursor, the doubly unsaturated hydrocarbon $C_{15}H_{24}$, is possibly represented by (VI).

The presence in alantolactone and isoalantolactone of two ethylenic linkages, as indicated by the hydrogenation and dehydrogenation experiments mentioned above, has been confirmed by the preparation of derivatives. Alantolactone forms a *dihydrochloride*, $C_{15}H_{22}O_2Cl_2$, m.p. 127–134° decomp., which, on boiling with alcohol, gives a *monohydrochloride*, m.p. 117°. A *dihydrobromide*, m.p. ca. 117° decomp., and a *monohydrobromide*, m.p. 106°, have also been prepared. isoAlantolactone gives a *dihydrochloride*, which has not yet been obtained crystalline.

It was concluded on the basis of the following evidence that one of the ethylenic linkages in both alantolactone and isoalantolactone must probably be in the $\alpha:\beta$ -position with respect to the potential carboxyl group. Alantolactone, its hydrochloride and dihydrochloride all afforded *dihydroalantolactone*, $C_{15}H_{22}O_2$, m.p. 123°, b.p. 195°/13 mm., *hydrochloride*, m.p. 120° decomp. on reduction with sodium amalgam, whilst, under the same conditions, isoalantolactone furnished a dihydroisoalantolactone, *hydrochloride*, m.p. 153°,* identical with that isolated from *Inula Helenium*. Both dihydroalantolactone and dihydroisoalantolactone gave with alkali the corresponding hydroxy acids, *dihydroalantolic acid*, $C_{15}H_{24}O_3$, *amide*, m.p. 186° decomp., and *dihydroisoalantolic acid*, $C_{15}H_{24}O_3$, m.p. 106–107°, *methyl ester*, m.p. 101°, *amide*, m.p. 176°.† The suggested presence of ethylenic linkages in the $\alpha:\beta$ -positions with respect to the carbonyls of the lactone groups in alantolactone and isoalantolactone was also supported by the fact that they formed *pyrazoline* derivatives, $C_{16}H_{22}O_2N_2$, with diazomethane, that from alantolactone, m.p. 116–117° decomp., from isoalantolactone,

* Hansen (*Ber.* 1931, **64**, 1904) states that dihydroisoalantolactone yields two hydrochlorides, m.p.s ca. 145° and ca. 135°.

† Bredt and Posth, *Annalen*, 1895, **285**, 356; Sprinz, *Ber.* 1901, **34**, 775; Hansen, *Ber.* 1931, **64**, 943.

m.p. 157° decomp., which cannot be reconverted by saponification back to the parent lactones.*

That dihydroisoalantolactone must be represented by the formula (VII) has been shown by its behaviour on oxidation. On ozonolysis formaldehyde and a *keto-lactone*, $C_{14}H_{20}O_3$ (VIII), m.p. $198-199^{\circ}$, *semicarbazone*, m.p. $232-233^{\circ}$, was obtained. The latter on reduction by the Clemmensen method afforded a saturated *acid*, $C_{14}H_{24}O_2$ (IX), b.p. $130-133^{\circ}/0.1$ mm., and a saturated *hydrocarbon*, $C_{13}H_{24}$ (X), m.p. -112° , b.p. $101-102^{\circ}/12$ mm., $d_4^{20} 0.8912$, $n_D^{20} 1.4811$, $[\alpha]_D^{20} -2.64^{\circ}$, identical with the 3-ethyl-9-methyl-cis-decalin which can be prepared from selinene. On dehydrogenation with selenium the hydrocarbon (X) gave β -ethyl-naphthalene (XII), *picrate*, m.p. $75-76^{\circ}$.† The presence of a semicyclic methylene group at the position indicated in formula (VII) for dihydroisoalantolactone, shown by the above experiments, has been confirmed by the following observations. When crude alantolactone, containing dihydroisoalantolactone, was subjected to ozonolysis and the product oxidised further with potassium permanganate a *ketonic acid*, $C_{10}H_{16}O_3$, m.p. $92-93^{\circ}$, b.p. $140-141^{\circ}/0.4$ mm., *semicarbazone*, m.p. $183-185^{\circ}$, *methyl ester, semicarbazone*, m.p. $207-208^{\circ}$, was obtained, which can be formulated as (XII), its formation proceeding *via* the unstable β -ketonic acid (XIII).‡ An additional product of the oxidation was the ketonic lactone (VIII), mentioned above. When this experiment was repeated using isoalantolactone probably containing some dihydroisoalantolactone, the keto-lactone (VIII), and a *ketonic acid*, $C_8H_{12}O_3$, *methyl ester semicarbazone*, m.p. 125° , probably (XIV), were formed.

Ruzicka and Pieth§ have provided evidence that dihydroalantolactone must be represented by (XV). On partial hydrogenation crude alantolactone afforded a *substance*, m.p. $129-136^{\circ}$, $[\alpha]_D -24.6^{\circ}$ (in alcohol), which was essentially dihydroalantolactone containing dihydroisoalantolactone and tetrahydroalantolactone as impurities. On ozonolysis this mixture gave the

* Hansen, *Ber.* 1931, **64**, 943.

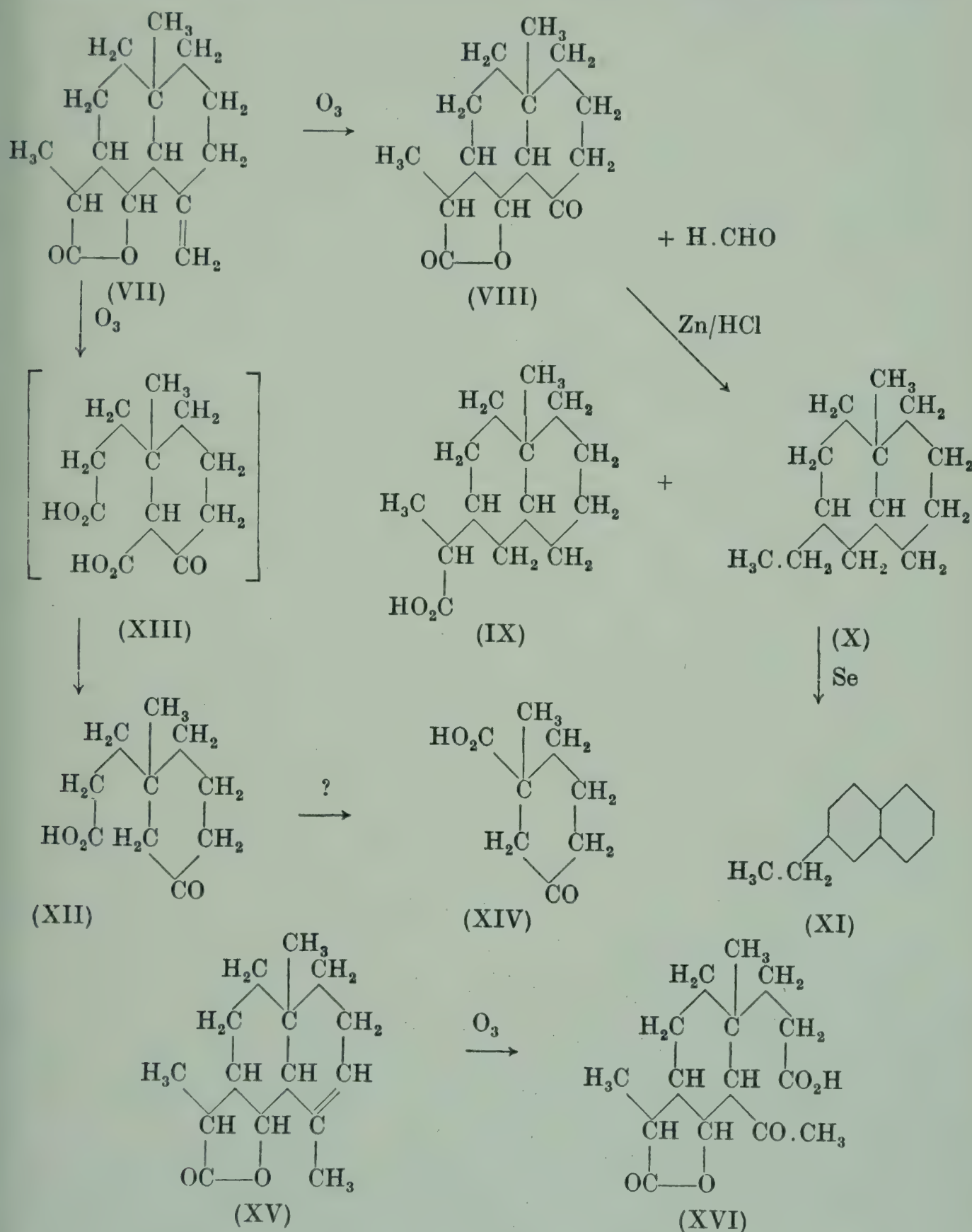
† Ruzicka and Pieth, *Helv. Chim. Acta*, 1931, **14**, 1090; Hansen, *Ber.* 1931, **64**, 1904.

‡ Ruzicka and Melsen, *Helv. Chim. Acta*, 1931, **14**, 397.

§ *Helv. Chim. Acta*, 1931, **14**, 1090; compare Ruzicka and Melsen, *ibid.* 1931, **14**, 397.

ketonic lactone (VIII) and also a lactonic *keto-acid*, $C_{15}H_{22}O_5$, *methyl ester*, b.p. 190–200°/0.4 mm., which must be formulated as (XVI). Hansen* has also prepared this acid (XVI), for which he finds m.p. 190–191°, by ozonolysis of dihydroalantolactone.

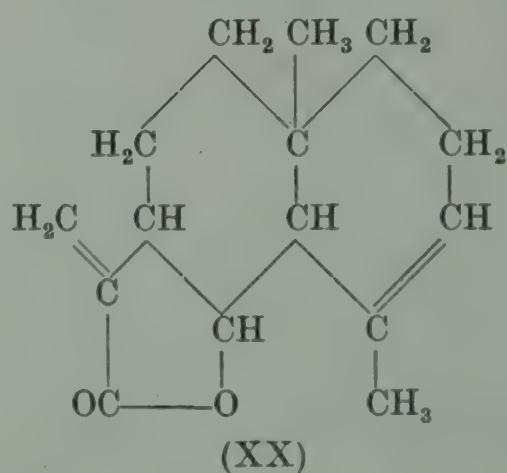
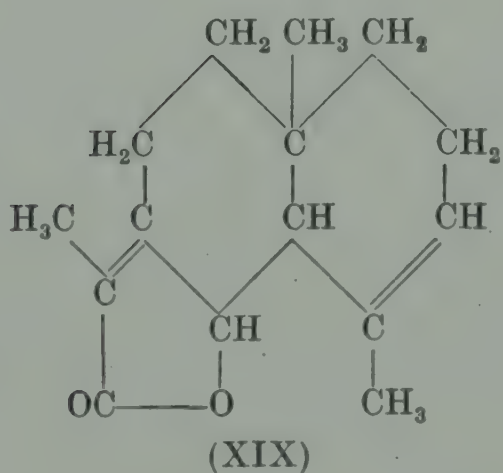
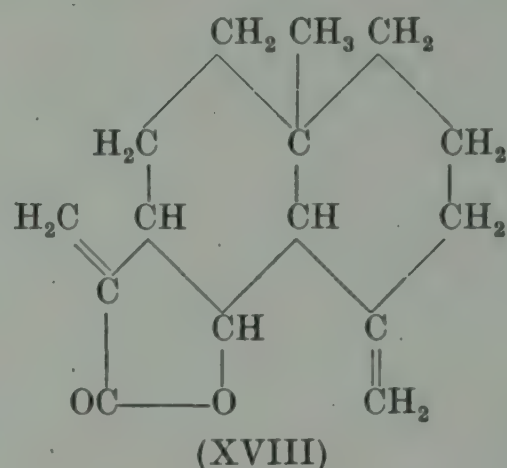
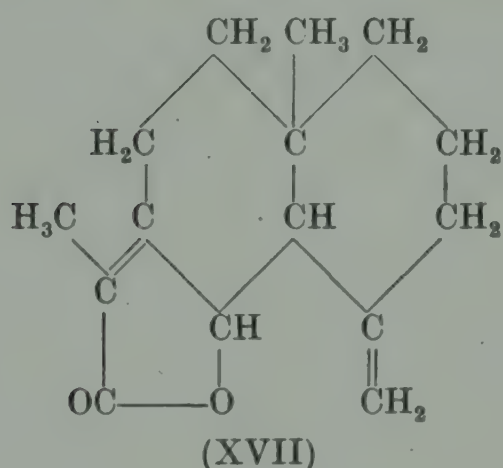
It has been shown by Hansen† that *isoalantolactone* gives on ozonolysis, followed by further oxidation with chromic acid,



* *J. pr. Chem.* 1933 [ii], 136, 176.

† *Ber.* 1931, 64, 1904.

acetic acid together with other non-volatile products. This, together with the other evidence detailed above, was taken to imply that *isoalantolactone* had the formula (XVII), the acetic acid being produced *via* pyruvic acid. It has, however, been observed by Ruzicka, Pieth, Reichstein and Ehmann* that the yield of acetic acid does not exceed 15–20 per cent. of the theoretical when *isoalantolactone* is ozonised, whereas in the case of *alantolactone* the yield is only about 5 per cent. of the theoretical. These results suggest that whilst neither of the lactones can be regarded as homogeneous, *isoalantolactone* corresponds more closely to (XVII) rather than to (XVIII) and *alantolactone* is possibly represented by (XIX) rather than alternative (XX). It is probably best, however, to regard *alantolactone* as a mixture of (XIX) and (XX) and *isoalantolactone* as a mixture of (XVII)



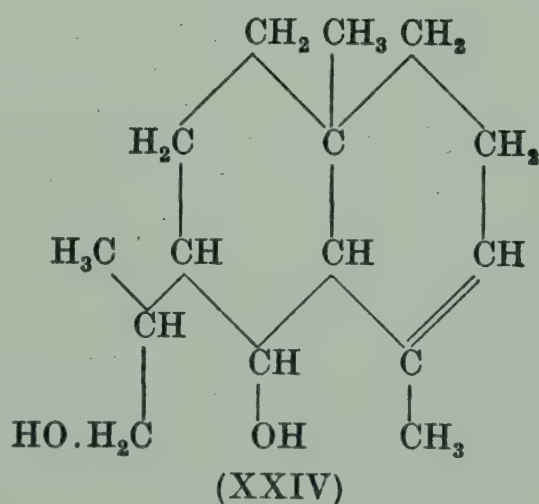
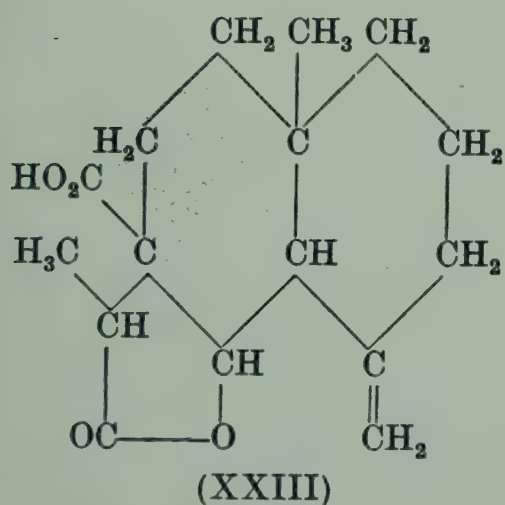
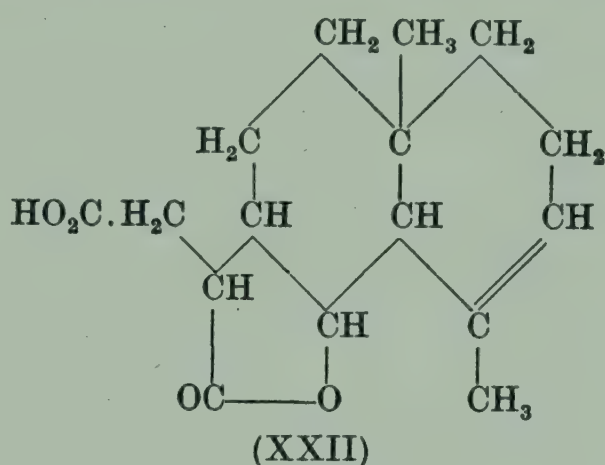
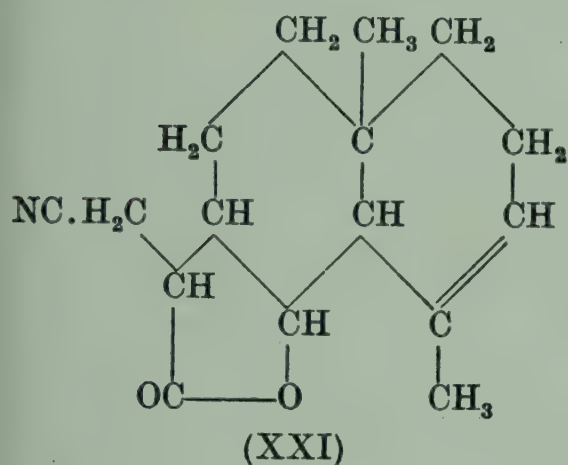
and (XVIII). They will then be mixtures of *isopropenyl* and *isopropylidene* derivatives as are so frequently encountered in terpene chemistry.

Alantolactone and *isoalantolactone* can be characterised by the preparation of the various derivatives to which reference has

* *Helv. Chim. Acta*, 1933, **16**, 268.

already been made. As might be expected of $\alpha:\beta$ -unsaturated lactones alantolactone and isoalantolactone combined with ammonia to give derivatives in which the addition is probably to the ethylenic linkage. The empirical formula of these adducts is still in doubt but it approximates to $(C_{15}H_{20}O_2)_2, NH_3$; that from alantolactone has m.p. $205-206^\circ$, *acetyl* derivative, m.p. 180° , from isoalantolactone m.p. 247° , *acetyl* derivative m.p. $216-217^\circ$.^{*} It has been suggested that the formation of these derivatives followed by their pyrolysis is a suitable method of preparing alantolactone and isoalantolactone in a state of purity.[†] The parent lactones cannot be regenerated by hydrolysis of these ammonia derivatives. Alantolactone is said to give a red colour with zinc chloride and iodine.[‡]

Alantolactone gives with hydrocyanic acid the *nitrile*, $C_{16}H_{21}O_2N$, possibly (XXI), m.p. 132° , which on hydrolysis affords the corresponding *carboxylic acid*, $C_{16}H_{22}O_4$, possibly (XXII), m.p. 137° , b.p. *ca.* $250^\circ/14$ mm.[§] Isoalantolactone



^{*} Hansen, *Ber.* 1931, **64**, 67; compare, however, Ruzicka and Pieth, *Helv. Chim. Acta*, 1931, **14**, 1090.

[†] Hansen, *loc. cit.*; see, however, Ruzicka and Pieth, *loc. cit.*

[‡] Tunmann, *Pharm. Zent.* 1912, **53**, 1176.

[§] Bredt and Kallen, *Annalen*, 1896, **293**, 352.

behaves in a similar fashion with the same reagents to furnish an isomeric *acid* $C_{16}H_{22}O_4$, possibly (XXIII), m.p. 174° .*

On reduction with sodium and alcohol alantolactone is converted to the *glycol*, $C_{15}H_{26}O_2$ (XXIV), b.p. $168-170^\circ/0.4$ mm.[†]

By heating tetrahydroalantolactone with sodium ethoxide at $170-180^\circ$ an isomeric *substance*, m.p. $60-61^\circ$ was obtained,[‡] the structure of which has not been determined.

COSTUS LACTONE AND RELATED LACTONES

From the higher boiling fractions of oil of costus (from the roots of *Saussurea Lappa* L.) Semmler and Feldstein[§] isolated an acid, *costus acid*, $C_{15}H_{22}O_2$, b.p. $200-205^\circ/11$ mm., $d^{21^\circ} 1.0508$, $n_D 1.5191$, $\alpha_D + 40^\circ$, *methyl ester*, b.p. $170-175^\circ/11$ mm., $d^{21^\circ} 1.0242$, $n_D 1.5106$, and two lactones, *costus lactone*, $C_{15}H_{20}O_2$, b.p. $205-211^\circ/13$ mm., $d^{21^\circ} 1.0891$, $n_D 1.5304$, $\alpha_D + 28^\circ$, and *dihydrocostus lactone*, $C_{15}H_{22}O_2$, b.p. $210-213^\circ/19$ mm., $d^{22^\circ} 1.0776$, $n_D 1.5229$, $\alpha_D + 48^\circ$. All three substances are bicyclic and contain two, two and one ethylenic linkages respectively. They are also closely related to each other for costus acid afforded dihydrocostus lactone on isomerisation with diluted sulphuric acid and both costus lactone and dihydrocostus lactone furnished the same *tetrahydrocostus lactone*, $C_{15}H_{24}O_2$, b.p. $198-202^\circ/13$ mm., $d^{21^\circ} 1.0451$, $n_D 1.5051$, $\alpha_D + 33^\circ$, on catalytic hydrogenation. Semmler and Feldstein^{||} also made the interesting observation that, when the methyl ester of costus acid was reduced with sodium and alcohol, it gave costol identical with the alcohol described under that name on p. 191.

A similar lactone to those described above was isolated by Ukita[¶] from the same source and investigated in more detail by Crabalona^{**} and by Naves.^{††} This substance, for which we propose the name *dehydrocostus lactone*, had the molecular formula $C_{15}H_{18}O_2$, and m.p. $63.5-64^\circ$, $d_4^{66^\circ} 1.0921$, $n_D^{66^\circ} 1.5333$, $[\alpha]_D - 13.7^\circ$ (in alcohol). It furnished the corresponding *hydroxy-acid*, $C_{15}H_{20}O_3$, m.p. 122° , and on hydrogenation with sodium and

* Hansen, *J. pr. Chem.* 1933 [ii], 136, 176.

† Ruzicka and Melsen, *Helv. Chim. Acta*, 1931, 14, 397.

‡ Hansen, *J. pr. Chem.* 1933 [ii], 136, 176.

§ *Ber.* 1914, 47, 2433.

|| *Ibid.* 1914, 47, 2687.

¶ *J. Pharm. Soc. Japan*, 1939, 59, 80.

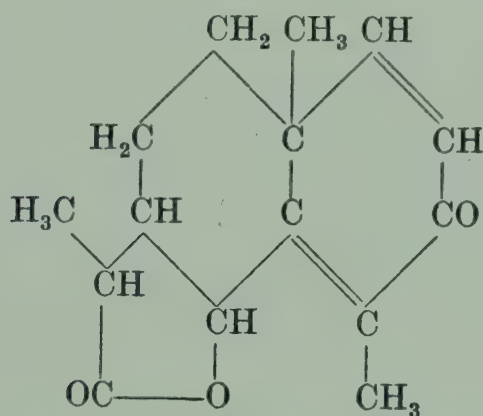
** *Bull. Soc. Chim.* 1948, 15, 357.

†† *Helv. Chim. Acta*, 1948, 31, 1172.

alcohol gave *dihydrodehydrocostus lactone*, b.p. 167–168°/1.6 mm., $d_4^{20^\circ}$ 1.0984, $n_D^{20^\circ}$ 1.5314, $[\alpha]_D + 38.9^\circ$, which may be identical with the original costus lactone of Semmler and Feldstein. Catalytic hydrogenation furnished *hexahydrodehydrocostus lactone*, $C_{15}H_{24}O_2$, b.p. 173–174°/3 mm., $d_4^{20^\circ}$ 1.0552, $n_D^{20^\circ}$ 1.5042, $[\alpha]_D + 54.4^\circ$, which may be identical with the tetrahydrocostus lactone described above. Dehydrocostus lactone must, therefore, be bicyclic and contain three ethylenic linkages. Two of the latter are present as methylenic groupings according to the ozonolysis evidence. Dehydrogenation of hexahydrodehydrocostus lactone gave ambiguous results. A mixture of S- and Se-guaiazulenes and a bicyclic *hydrocarbon*, $C_{15}H_{26}$, b.p. 84°/2 mm., $d_4^{20^\circ}$ 0.8766, $n_D^{20^\circ}$ 1.4775, appeared to be formed. The action of heat on dehydrocostus lactone causes isomerisation to an amorphous substance.

B. KETO-LACTONES AND HYDROXY KETO-LACTONES

SANTONIN (*l*-SANTONIN)



The various species of *Artemisia* found widely distributed in nature, and more particularly in the Volga district of Russia, in Turkestan, in Persia and in the North-West frontier area of India, have been found to contain several closely related lactones, santonin, β -santonin (p. 320), ψ -santonin (p. 322) and artemisin (p. 312). Of these santonin, or *l*-santonin as it is sometimes termed, is by far the most abundant, occurring to the extent of several per cent. in the leaves and especially in the immature flower buds (wormseed or *flores cinae*).^{*} The principal species of

^{*} For example, see Krishna and Varma, *Quart. J. Pharm. Pharmacol.* 1933, 6, 23; Quazilbash, *ibid.* 1942, 15, 323.

Artemisia used for the extraction of santonin is said to be *A. Cina* Berg (*A. maritima* Linn.),* but santonin has also been found in *A. brevifolia* Wallich,[†] *A. mexicana* Willd., *A. neo-mexicana* Wooton, *A. Wrightii*,[‡] *A. coeresculens*,[§] *A. fragrans* Willd., *A. pauciflora* Weber^{||} and in *A. gallica* Willd.[¶] It is present in species of *Artemisia* native to the British Isles** and in European specimens.^{††} Because of its powerful anthelmintic action santonin is widely used in medicine.

Santonin, $C_{15}H_{18}O_3$, which crystallises from alcohol or water in flat hexagonal prisms, m.p. 171–172°, $[\alpha]_D^{18} - 173^\circ$ (in alcohol), $[\alpha]_D - 171.7^\circ$ (in methyl alcohol), $[\alpha]_D^{15} - 171.7^\circ$ (in chloroform),^{‡‡} was first isolated from wormseed by Kahler in 1830.^{§§}

Much of the earlier work on the chemistry of santonin was carried out by Cannizzaro, Andreocci, Gucci, Francesconi, and other Italian chemists during the decades prior to 1910, and numerous formulae were from time to time proposed for the substance. It was not, however, until it was realised that santonin readily undergoes rearrangement with the somewhat unexpected migration of a methyl group that the correct constitutional formula was proposed by Clemo, Haworth and Walton in 1929.

It was realised from the earliest days of santonin chemistry that it must be an unsaturated ketonic lactone, for it dissolved readily in alkalis to give the salts of *santoninic acid*, $C_{15}H_{20}O_4$, $[\alpha]_D^{22.5} - 25.9^\circ$ (in alcohol), *oxime*, m.p. 80°, *methyl ester oxime*, two forms m.p.s 184° and 196°, from which it could be regenerated

* For example, see Janot and Gautier, *Bull. Sci. Pharmacol.* 1935, **42**, 404; Coutts, *Quart. J. Pharm. Pharmacol.* 1936, **9**, 357.

† Greenish and Pearson, *Pharm. J.* 1921, **106**, 2; Greenish and Maplethorpe, *ibid.* 1923, **111**, 127; *Chemist and Druggist*, 1923, **99**, 147; Simonsen, *Pharm. J.* 1923, **111**, 632.

‡ Viehoveer and Capen, *Am. J. Pharm.* 1922, **94**, 446; *J. Amer. C.S.* 1923, **45**, 1941.

§ Herndlhofer, *Mikrochem.* 1927, **5**, 21.

|| Quazilbash, *Bull. Sci. Pharmacol.* 1935, **42**, 129.

¶ Coutts, *Quart. J. Pharm. Pharmacol.* 1934, **7**, 392; compare Heckel and Schlagdenhauffen, *Compt. rend.* 1885, **100**, 805.

** *Inter al.* Coutts, *Pharm. J.* 1929, **123**, 603; *Quart. J. Pharm. Pharmacol.* 1934, **7**, 392; 1936, **9**, 357.

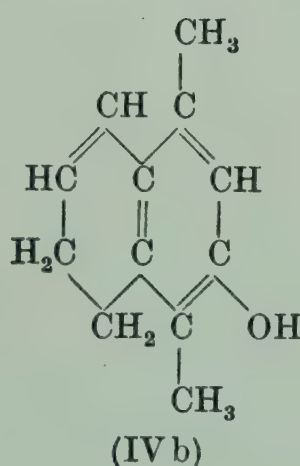
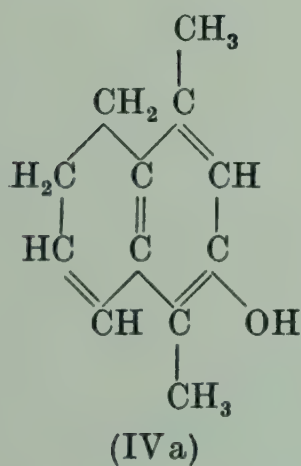
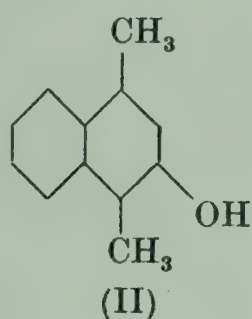
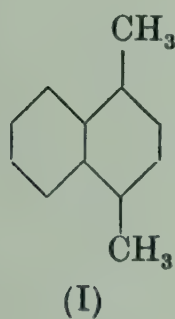
†† However compare Janot and Cormier, *Bull. Sci. Pharmacol.* 1942, **49**, 157.

‡‡ Compare Hauser, *Arch. Pharm.* 1941, **279**, 175; Green, *Bull. Nat. Form. Comm.* 1944, **12**, 177.

§§ *Arch. Pharm.* 1830, **34**, 318; 1830, **35**, 216; compare Alms, *ibid.* 1830, **34**, 319; 1831, **39**, 190; Oberdörffer, *ibid.* 1830, **35**, 219; Heldt, *Annalen*, 1847, **63**, 10.

unchanged by acidification, and it readily furnished the usual derivatives characteristic of the ketone grouping (see p. 269).*

Proof of the main features of the carbon skeleton present in santonin resulted from a number of independent investigations, which are briefly summarised below. In a series of interesting experiments Cannizzaro and Carnelutti[†] showed that santonin on distillation with zinc dust afforded 1:4-dimethylnaphthalene (I), propylene and some 1:4-dimethylnaphth-2-ol (II). They also found that santonin could be reduced by treatment with red phosphorus and hydriodic acid[‡] to a mixture of two isomeric phenolic acids, *d*-santonous acid and *dl*-santonous acid, $C_{15}H_{20}O_3$, the formation and chemistry of which are fully discussed on pp. 265–8. By a similar zinc dust distillation *d*-santonous acid gave 1:4-dimethylnaphthalene (I), propylene, 1:4-dimethylnaphth-2-ol (II), and a small amount of *p*-xylene (III), whilst Andreocci[§] showed that *dl*-santonous acid furnished (I) by this process. The simple pyrolysis of *d*-santonous acid at 300–360°^{||} gave a mixture of products including (I), (II), propionic acid



* Tromsdorff, *Annalen*, 1834, **11**, 196; Heldt, *ibid.* 1847, **63**, 15, 24; Hesse, *Ber.* 1873, **6**, 1280; compare Lepage, *Jahresber.* 1876, p. 618; Simmer, *Arch. Pharm.* 1906, **244**, 679.

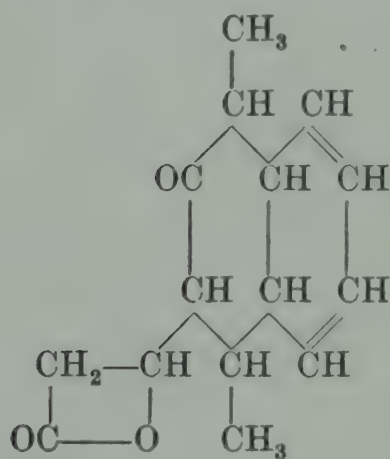
[†] *Ber.* 1879, **12**, 1574; *Atti R. Accad. Lincei, Transunti*, 1879 [iii], **3**, 241; *Ber.* 1880, **13**, 1516; *Gazz.* 1883, **12**, 393, 401, 414; 1884, **13**, 385.

[‡] See also Bertolo, *Gazz.* 1926, **56**, 859.

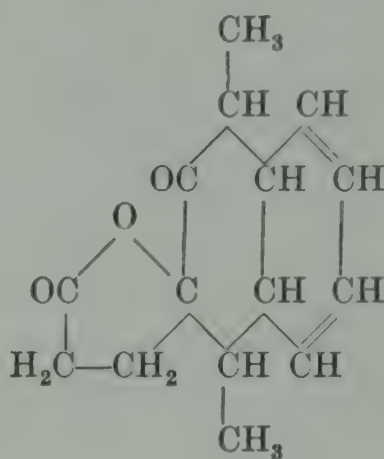
[§] *Gazz.* 1882, **12**, 410.

^{||} Similar products are obtained by the thermal decomposition of ethyl *d*-santonite; see Rizzo, *Gazz.* 1895, **25**, II, 292.

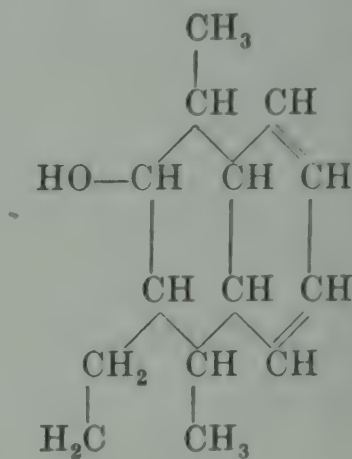
and the so-called *ar-dihydro-1:4-dimethylnaphth-2-ol*, probably (IV a) or (IV b) and its *propionate*. *ar*-Dihydro-1:4-dimethylnaphth-2-ol gave (I) on heating with phosphorus pentasulphide and (II) on heating with sulphur, thus indicating its relationship to the other decomposition products of santonin. Both *d*- and *dl*-santonous acids afforded (II) on heating with barium hydroxide at 360°. As a result of these investigations Cannizzaro* suggested the formulae (V) or (VI) for santonin and (VII) for



(V)



(VI)



(VII)

its reduction product, santonous acid. It will be noted that the lactone grouping in these early formulae for santonin was placed in the same ring as the carbonyl group and the two methyl groups.

The experiments of Gucci† showed these formulae to be incorrect.‡ When santonin β -oxime (see p. 269) was reduced by zinc dust and alcoholic sulphuric acid it furnished the corresponding primary amine, *santoninamine*, $C_{15}H_{21}O_2N$, m.p. 96°, *hydrochloride*, m.p. 199°, $[\alpha]_D^{11} - 136.8^\circ$ (in water), *sulphate monohydrate*, m.p. 145–146°, $[\alpha]_D^{10} - 103.7^\circ$ (in water), which, by treatment with nitrous acid or simply by boiling with water, was converted *via* the corresponding secondary alcohol and with loss of water to a lactone, *hyposantonin*, $C_{15}H_{18}O_2$, m.p. 152–153°, $[\alpha]_D + 32.7^\circ$ (in benzene). Hyposantonin together with its stereoisomer, *isohyposantonin*, m.p. 168.5°, $[\alpha]_D - 70.3^\circ$ (in benzene), were obtained similarly by reduction of santonin β -oxime, its acetate (see p. 269) or of santonin phenylhydrazone

* *Ber.* 1885, 18, 2746.† *Gazz.* 1889, 19, 378, 392.‡ Compare Gucci and Grassi-Cristaldi, *Atti R. Accad. Lincei*, 1891 [iv], 7, II, 35; *Gazz.* 1892, 22, I, 3, 24, 35, 44.

(see p. 271) with sodium amalgam. Hyposantonin was readily converted to *isohyposantonin* by dissolution in alkali followed by reprecipitation with acid, or in other ways, and the chemistry of these two stereoisomers is discussed further on p. 291. Both hyposantonin and *isohyposantonin* afforded 3:6-dimethylphthalic acid (VIII) on oxidation with potassium permanganate. Since, presumably, the lactonic grouping of these stereoisomers is the same as that in santonin, it is obvious that this grouping cannot be in the same ring as the two methyl groups and therefore as the ketonic oxygen atom.

Hyposantonin and *isohyposantonin* are lactones of the corresponding hydroxy acids, *hyposantoninic acid*, $[\alpha]_D - 4.6^\circ$ (in alcohol) and *isohyposantoninic acid*, $[\alpha]_D + 71.6^\circ$ (in alcohol), $C_{15}H_{20}O_3$, and, as implied by this relationship, can be isomerised, by treatment with alcoholic hydrochloric acid, to two acids, $C_{15}H_{18}O_2$, known respectively as *dihydrosantonic acid*, m.p. 120–121°, $[\alpha]_D + 62.1^\circ$ (in alcohol), and *isodihydrosantonic acid*, m.p. 96–97°, optically inactive. On heating with barium hydroxide dihydrosantonic acid gave 1:4-dimethyl-7-ethylnaphthalene (IX). When hyposantonin, *isohyposantonin* or dihydrosantonic acid were oxidised with iodine in acetic acid solution they all afforded the naphthalene derivative, *santonic acid*, $C_{15}H_{16}O_2$, m.p. 132°, $[\alpha]_D^{16^\circ} + 64.4^\circ$ (in alcohol), whilst *isodihydrosantonic acid* in the same way gave *isosantonic acid*, m.p. 132.5–133°, optically inactive. Like dihydrosantonic acid, santonic acid also furnished 1:4-dimethyl-7-ethylnaphthalene (IX), on heating with barium hydroxide. These experiments established, therefore, the position of the acidic side chain in santonic acid and led to the suggestion by Gucci and Grassi-Cristaldi that santonin should be represented by (X), when santoninamine would be (XI), hyposantonin (XII), hyposantoninic acid (XIII), dihydrosantonic acid (XIV), and santonic acid (XV), their interrelationships being illustrated in the scheme on p. 254.

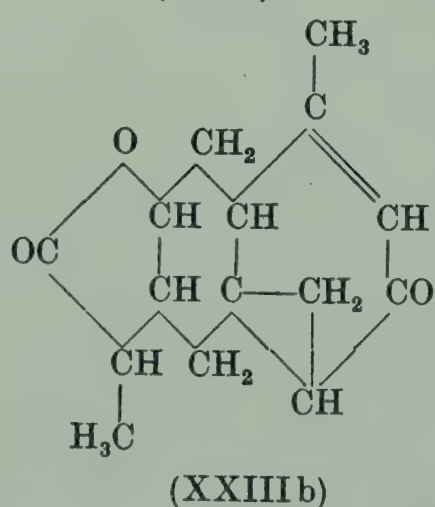
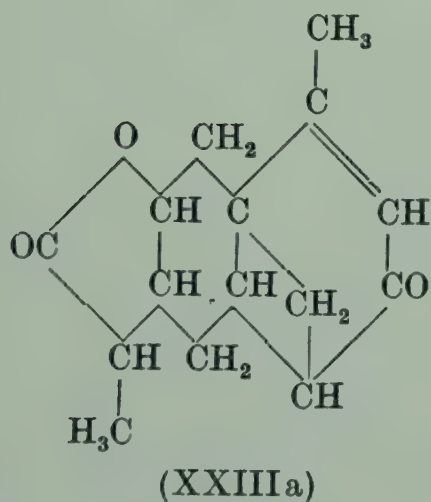
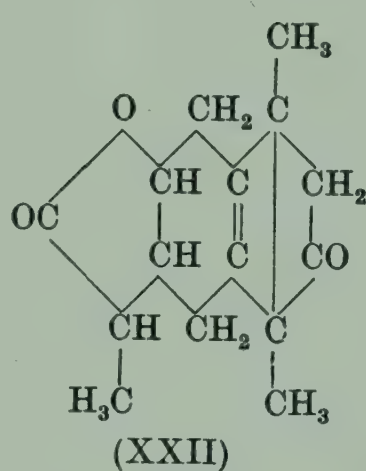
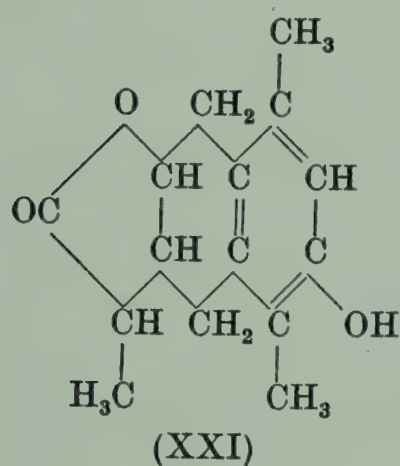
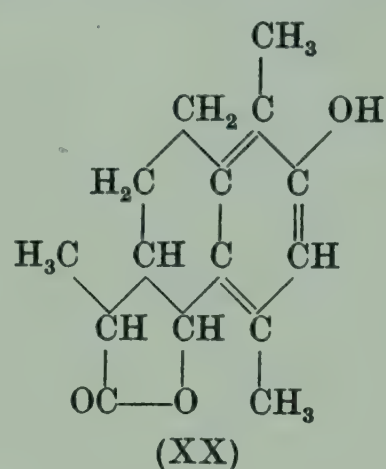
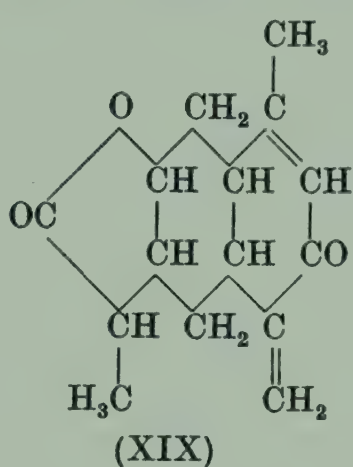
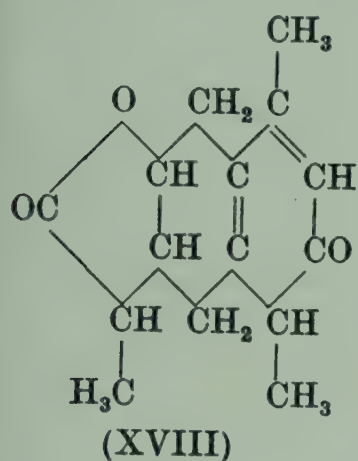
An alternative (XVI), to the formula of Gucci and Grassi-Cristaldi was proposed by Cannizzaro and Gucci,* which explained equally well the known experimental facts. This formula was also preferred by Andreocci,† although he suggested

* *Atti R. Accad. Lincei*, 1892 [v], 1, II, 149; *Gazz.* 1893, 23, I, 286.

† *Ber.* 1893, 26, 1373.

at the same time that the variant (XVII) was equally satisfactory.

From time to time various alternatives to these formulae for santonin were proposed. Thus Bargellini* suggested the formula (XVIII), whilst Francesconi and Cusmano† thought that (XIX) was preferable. It will be noted, however, that all these formulae are simply the hypothetical ketonic tautomerides of the corresponding phenols. Thus (X) might be rewritten as (XX) and (XVI) as (XXI) and so on. In view of the absence of phenolic properties in santonin and to explain the results of his degrada-



* *Atti R. Accad. Lincei*, 1907 [v], 16, II, 264.

† *Ibid.* 1908 [v], 17, I, 66; *Gazz.* 1908, 38, II, 109.

tion experiments on santonic acid (see p. 295), Francesconi* suggested the formula (XXII), which contained four rings and only one double bond. The alternative formulae (XXIIIa) or (XXIIIb) were later proposed by Angeli and Marino.†

The doubts as to the tricyclic nature of the santonin molecule raised by these suggestions were conclusively disproved by the study of the behaviour of santonin on catalytic hydrogenation.‡ Santonin readily takes up two molecules of hydrogen under the usual conditions of catalytic hydrogenation to give a mixture of two saturated ketonic lactones, $C_{15}H_{22}O_3$, α -*tetrahydrosantonin*, m.p. 156° , $[\alpha]_D + 13^\circ$ (in methyl alcohol), $+ 23.4^\circ$ (in alcohol), $+ 28.0^\circ$ (in chloroform),§ *oxime*, m.p. $235-237^\circ$, $[\alpha]_D$ ca. -45° (in chloroform), *semicarbazone*, m.p. $256-258^\circ$ decomp., *phenylhydrazone*, m.p. 205° decomp., and β -*tetrahydrosantonin*, m.p. 105° , $[\alpha]_D^{18^\circ} + 9.3^\circ$ (in methyl alcohol), *oxime*, m.p. 182° , $[\alpha]_D^{20^\circ} - 18.0^\circ$ (in chloroform), *semicarbazone*, m.p. $248-250^\circ$ decomp. The hydrogenation of santonic acid similarly affords a mixture of α -*tetrahydrosantoninic acid*, $C_{15}H_{24}O_4$, m.p. 115° , $[\alpha]_D + 20^\circ$ (in methyl alcohol) and β -*tetrahydrosantoninic acid*, $C_{15}H_{24}O_4$, m.p. 200° decomp., $[\alpha]_D + 2.2^\circ$ (in methyl alcohol), *oxime*, m.p. $218-220^\circ$. By the action of heat these acids are transformed with loss of water into α - and β -*tetrahydrosantonins* respectively, from which they can also be obtained by the action of alkali.¶ It was concluded therefore that santonin must contain two carbon rings and two ethylenic linkages.

The ready conversion of santonin oxime and of santoninamine into compounds containing an aromatic nucleus merely by the equivalent of dehydration (see pp. 253, 254) suggested that the two double bonds of santonin are probably situated in the same carbon ring as the ketonic oxygen atom. Support for this view

* *Atti R. Accad. Lincei*, 1896 [v], 5, II, 217; *Gazz.* 1899, 29, II, 182, 211, 212; compare Klein, *Arch. Pharm.* 1893, 231, 695.

† *Atti R. Accad. Lincei*, 1907 [v], 16, I, 157; compare *Atti R. Accad. Lincei Memorie*, 1897 [v], 6, 389.

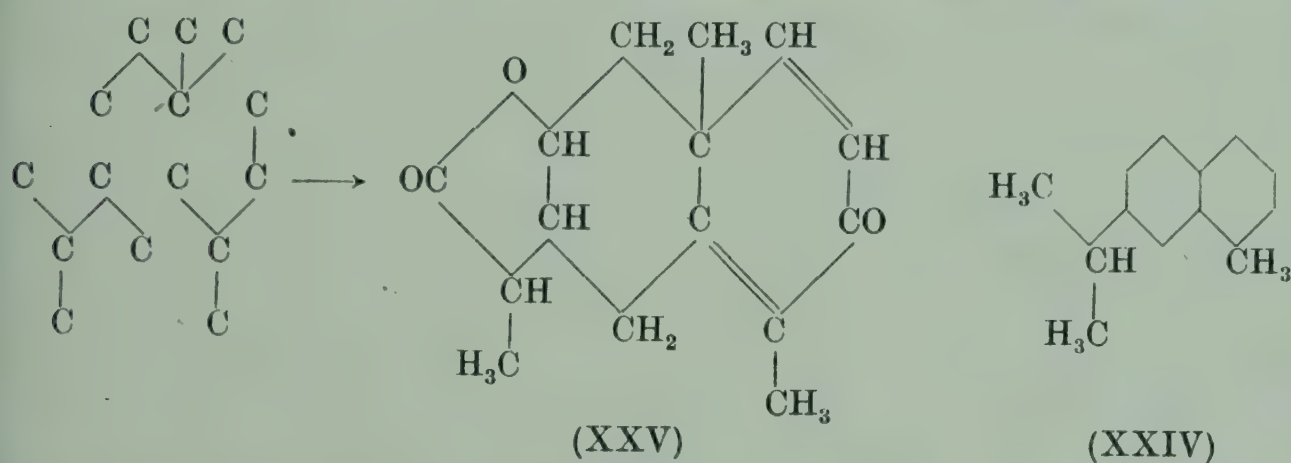
‡ Wienhaus and Oettingen, *Annalen*, 1913, 397, 219; Wienhaus, *Ber.* 1913, 46, 2839; Wedekind and Beniers, *Annalen*, 1913, 397, 246; Asahina, *Ber.* 1913, 46, 1775; Bargellini, *Atti R. Accad. Lincei*, 1913 [v], 22, I, 443; Rimini and Jona, *Rend. Soc. Chim. Ital.* 1913 [ii], 5, 52; compare Cusmano, *Atti R. Accad. Lincei*, 1913 [v], 22, I, 507, 711; Wedekind, Goost and Jackh, *Ber.* 1930, 63, 50.

§ Bargellini, *loc. cit.* quotes $[\alpha]_D^{17^\circ} + 61.5^\circ$ (in alcohol) and Asahina, *loc. cit.* records $[\alpha]_D^{25^\circ} + 60.6^\circ$ (in chloroform); the values given here are from the papers of Wienhaus and Oettingen and of Wedekind and Beniers.

¶ Wienhaus and Oettingen, *loc. cit.*

was provided by the observation that on treatment with fuming hydrochloric acid in the cold santonin was isomerised to a phenolic lactone, *d-desmotroposantonin*, m.p. 260° , $[\alpha]_D^{10} + 112.7^{\circ}$ (in alcohol), *methyl ether*, m.p. $152-153^{\circ}$, $[\alpha]_D^{27} + 91.9^{\circ}$ (in alcohol), *ethyl ether*, m.p. 168° , $[\alpha]_D^{28} + 114.2^{\circ}$ (in alcohol), *benzyl ether*, m.p. $181-182^{\circ}$, $[\alpha]_D + 102.6^{\circ}$ (in alcohol), *acetate*, m.p. 154° , $[\alpha]_D^{18} + 92.5^{\circ}$ (in alcohol), $[\alpha]_D^{24} + 93.6^{\circ}$ (in acetic acid).^{*} *d*-Desmotroposantonin is formed similarly by the action of hydrobromic acid or of hot dilute sulphuric acid on santonin.[†] The chemistry of *d*-desmotroposantonin and its stereoisomers is discussed more fully on p. 263.

The first serious criticism of the various formulae that had been proposed for santonin was made by Clemo, Haworth and Walton.[‡] These authors pointed out that, although santonin was presumably a sesquiterpene derivative, none of the previously proposed formulae could be regarded as being built up from three isoprene residues. They suggested that santonin might be a derivative of eudalene (XXIV) and be represented by (XXV). It was further suggested that the formation of *d*-



desmotroposantonin (formulated as (XXVI)), from santonin must involve a migration of the quaternary methyl group in analogy with the known rearrangement of the compound (XXVII) to (XXVIII) under comparable conditions.[§]

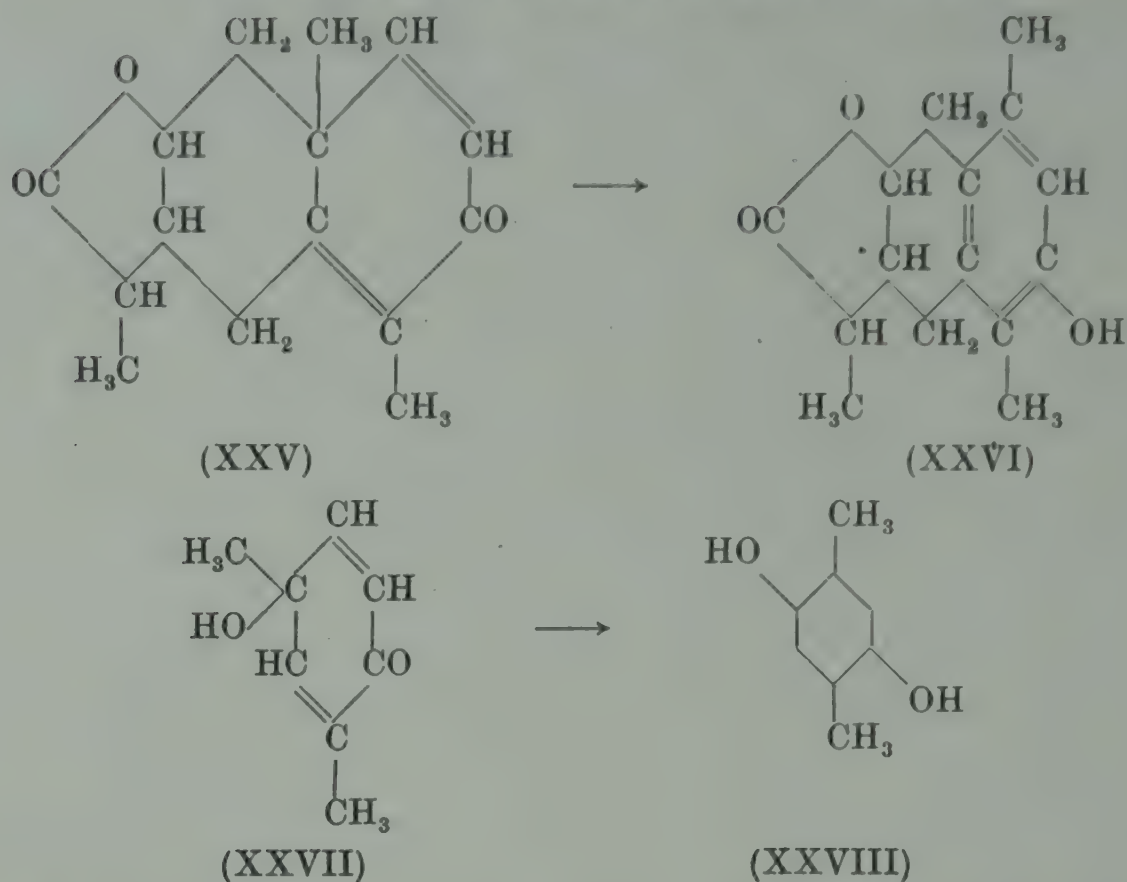
Clemo, Haworth and Walton then synthesised *dl*-santonous acid and showed it to be represented by (XXIX) in agreement

^{*} Andreocci, *Gazz.* 1893, **23**, II, 469; 1895, **25**, I, 475, 481; 1899, **29**, I, 514; *Atti R. Accad. Lincei*, 1899 [v], **8**, I, 81; compare Wedekind, *Ber.* 1898, **31**, 1677.

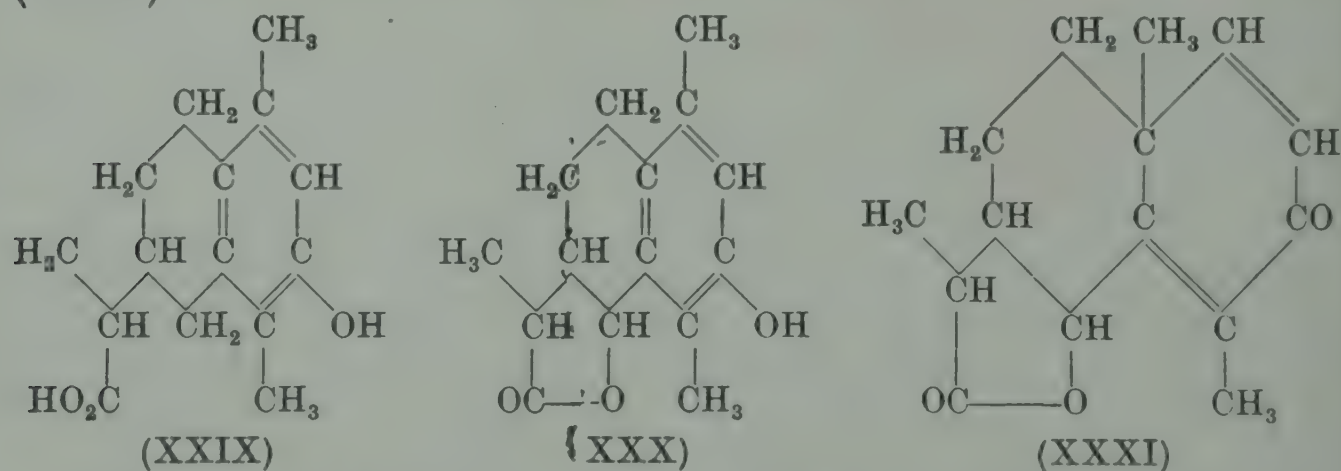
[†] Angeli and Marino, *Atti R. Accad. Lincei, Memorie*, 1897 [v], **6**, 390; Bargellini and Mannino, *Gazz.* 1909, **39**, II, 103.

[‡] *J.C.S.* 1929, p. 2368.

[§] See Bamberger and Brady, *Ber.* 1900, **33**, 3642.



with the views of many previous workers. This synthesis confirmed the position of the propionic acid residue in santonin (see previous formulae), but it did not, of course, offer any evidence as to the position of fusion of the lactone ring. In a later communication Clemo, Haworth, and Walton* proved by the synthesis of racemic desmotroposantonin that this substance was correctly represented by (XXX) and not by (XXVI),† so that santonin was to be represented by (XXXI) and not (XXV).

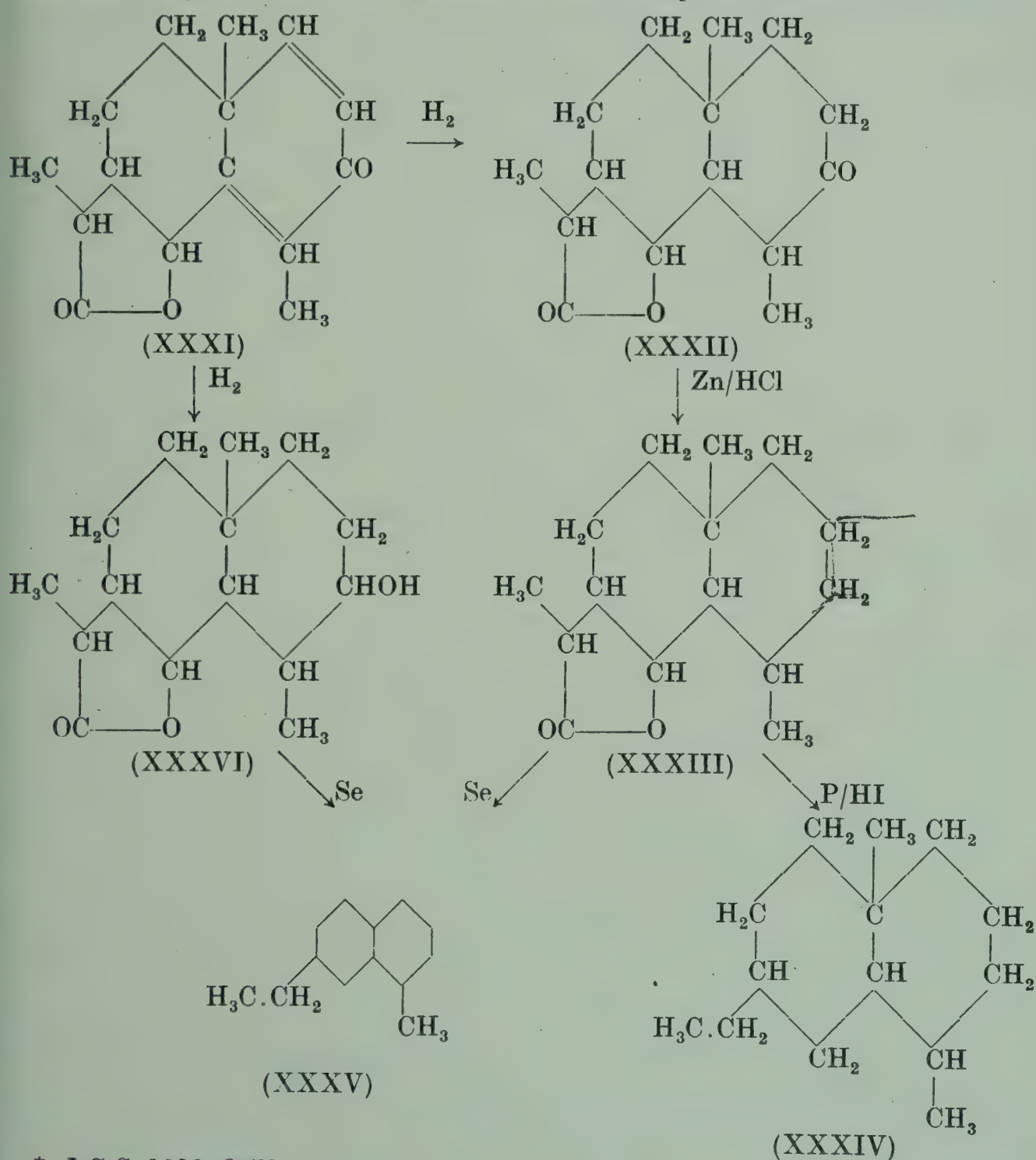


Further proof of the correctness of the formula (XXXI) for santonin was provided by the experiments of Clemo and

* *Loc. cit.*

† See also Tschitschibabin and Sechtschukina (*Ber.* 1930, **63**, 2793), who have likewise synthesised racemic desmotroposantonin and compare Bergs (*Ber.* 1930, **63**, 1285).

Haworth,* who reduced α -tetrahydrosantonin (XXXII), by the Clemmensen method to *deoxytetrahydrosantonin*, $C_{15}H_{26}O_2$ (XXXIII), m.p. 141–142°.† This deoxy compound could be reduced by red phosphorus and hydriodic acid to a *dimethylethyl-decalin*, presumably (XXXIV), b.p. 120–125°/20 mm. Although attempts to dehydrogenate this latter compound were unsuccessful, deoxytetrahydrosantonin itself was easily dehydrogenated by heating with selenium to give 1-methyl-7-ethyl-naphthalene (XXXV), *picrate*, m.p. 94°, *styphnate*, m.p. 126°. The same hydrocarbon was also obtained by Ruzicka and Eichen-



* *J.C.S.* 1930, 2579.

† Compare Wedekind and Tettweiler, *Ber.* 1931, 64, 387, who found m.p. 153–154°.

berger* by catalytic hydrogenation of santonin to the secondary alcohol *hexahydrosantonin*, $C_{15}H_{24}O_3$ (XXXVI), m.p. 210–211°, and dehydrogenation of this substance with selenium.

The oxidative degradation of santonin and santoninic acid has provided valuable proof that the angular methyl group eliminated in the dehydrogenations described above is indeed at the position suggested in formula (XXXI).† On treatment with perbenzoic acid or hydrogen peroxide in acetic acid solution santonin afforded a mixture of two stereoisomeric oxides (XXXVII), $C_{15}H_{18}O_4$, *santonin* α -oxide, m.p. 214°, $[\alpha]_D^{18} - 108.6^\circ$ (in chloroform), *phenylhydrazone*, m.p. 176–178° decomp., and *santonin* β -oxide, m.p. 157°, *phenylhydrazone*, m.p. ca. 280°.‡ On ozonolysis santonin α -oxide afforded an *ozonide*, $C_{15}H_{18}O_6$, m.p. 189°, which, by boiling with water, was decomposed to give a ketonic *dicarboxylic acid*, $C_{15}H_{18}O_7$, m.p. 207–208°, *oxime*, m.p. 228° decomp., *quinoxaline* derivative, m.p. 289° decomp., to be formulated as (XXXVIII). The same dicarboxylic acid was also obtained by direct ozonolysis of santonin and indirectly from santoninic acid by oxidation with potassium permanganate. By oxidation with this latter reagent santoninic acid afforded *dihydroxysantoninic acid*, $C_{15}H_{22}O_6$ (XXXIX), readily dehydrated to *dihydroxysantonin*, $C_{15}H_{20}O_5$ (XL), m.p. 261°, and oxidised further by potassium permanganate to the dicarboxylic acid (XXXVIII), *bisphenylhydrazone*, m.p. 100°. This acid (XXXVIII) was also obtained directly by the oxidation of santoninic acid with potassium permanganate; by oxidation with lead peroxide it afforded a *dicarboxylic acid*, $C_{14}H_{18}O_6$, *bisphenylhydrazone*,§ m.p. 114–116° decomp., presumably (XLI).

* *Helv. Chim. Acta*, 1930, **13**, 1117.

† Angeli and Mannino, *Atti R. Accad. Lincei, Memorie*, 1907 [v], **6**, 385; *Ber.* 1913, **46**, 2233; Bargellini and Gialdini, *Atti R. Accad. Lincei*, 1908 [v], **17**, **1**, 248; Wedekind, *Ber.* 1915, **48**, 891; Angeli and Mannino, *Atti R. Accad. Lincei*, 1924 [v], **33**, **II**, 10; compare Heldt, *Annalen*, 1847, **63**, 46; Wagner, *Ber.* 1887, **20**, 1664; Francesconi, *Gazz.* 1899, **29**, **II**, 206; Montemartini, *ibid.* 1902, **32**, **I**, 354; Angeli and Mannino, *Atti R. Accad. Lincei*, 1907 [v], **16**, **I**, 160; Wedekind and Tettweiler, *Ber.* 1931, **64**, 1796.

‡ Wedekind and Koch (*Ber.* 1905, **38**, 1849) originally called santonin α -oxide δ -hydroxysantonin and it has also been known as isoartemisin; Cusmano (*Atti R. Accad. Lincei*, 1918 [v], **27**, **I**, 118; *Gazz.* 1918, **48**, **I**, 248) apparently prepared santonin β -oxide by the hydrogen peroxide method and called it ϵ -hydroxysantonin. These misleading names should now be deleted from the literature.

§ The constitution of this bisphenylhydrazone is not at all clear on the basis of the formula (XLI); the same applies to the bisphenylhydrazone of the dicarboxylic acid (XXXVIII).



On further oxidation with potassium permanganate the ketonic dicarboxylic acid (XXXVIII) furnished a *tetracarboxylic acid*, $C_{11}H_{16}O_8$ (XLII), m.p. $165-166^\circ$ decomp., which lost carbon dioxide and water at 170° to give a tricarboxylic acid *anhydride*, $C_{10}H_{14}O_5$, presumably (XLIII), m.p. $145-146^\circ$, *chloride*, b.p. $150^\circ/0.1$ mm., furnishing the corresponding *tricarboxylic acid*, $C_{10}H_{16}O_6$ (XLIV), m.p. 127° , *di-p-anisidide*, m.p. $182-185^\circ$, *α -naphthylimide*, m.p. $147-147.5^\circ$. Ruzicka and Steiner* have confirmed the formulation of this tricarboxylic acid as *heptane-2:3:6-tricarboxylic acid* by direct synthesis. On further oxidation with chromic acid (XLIV) afforded a *tricarboxylic acid*, $C_8H_{12}O_6$, m.p. 110° , which should, presumably, be formulated as (XLV).

The α - and β -santonin oxides mentioned above are readily catalytically hydrogenated, each oxide yielding two stereoisomeric dihydrosantonin oxides, $C_{15}H_{20}O_4$,[†] *α -dihydrosantonin α -oxide* (XLVI), m.p. $142-143^\circ$, *oxime*, m.p. 225° decomp., *β -dihydrosantonin α -oxide*, m.p. 169° , *oxime*, m.p. $189-190^\circ$ decomp., *α -dihydrosantonin β -oxide*, m.p. 146° and *β -dihydrosantonin β -oxide*, m.p. 117° . By the action of ozone α -dihydrosantonin α -oxide (XLVI) was converted into a ketonic *dicarboxylic acid*, $C_{15}H_{20}O_7$ (XLVII), m.p. 174° , which could also be obtained by the catalytic hydrogenation of the keto-dicarboxylic acid (XXXVIII).

Paranjape, Phalnikar, Bhide and Nargund[‡] have recently made the extraordinary claim to have effected the synthesis of an optically active santonin identical with naturally occurring santonin without use of an asymmetric reagent or similar device. This synthesis, for details of which the original papers should be consulted, has been severely criticised by *inter al.* Cornforth, Cornforth and Dewar,[§] O'Gorman,^{||} and by Clemo, Cocker and Hornsby[¶] and there can be no doubt that it is incorrect.

It will be seen from the formula (XXXI) for santonin that a substance of this constitutional formula should theoretically be

* *Helv. Chim. Acta*, 1934, **17**, 614.

† Wedekind and Tettweiler, *Ber.* 1931, **64**, 387, 1796.

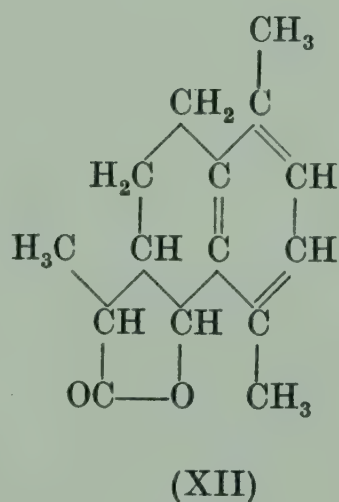
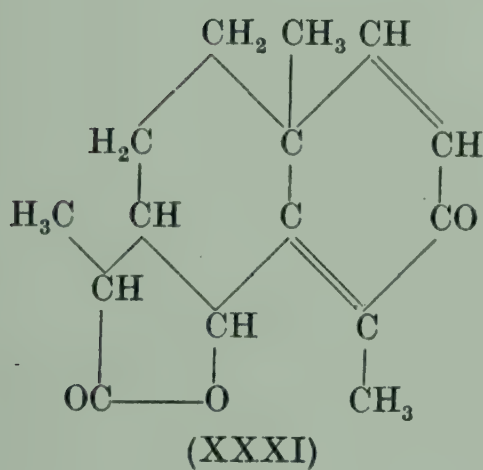
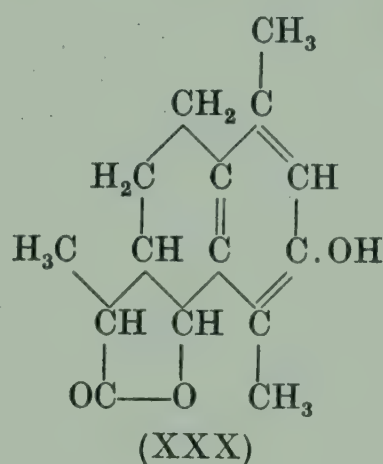
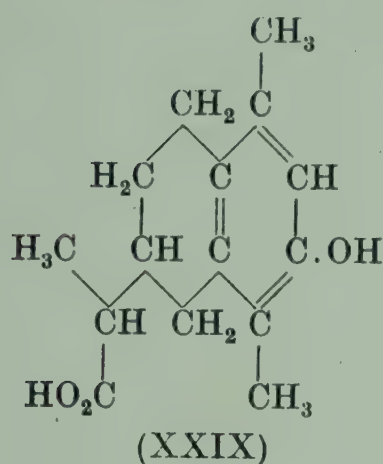
‡ *Current Sci.* 1943, **12**, 150; *Rasayanam*, 1943, **1**, 233; *Nature*, 1944, **153**, 141; *Proc. Ind. Acad. Sci.* 1944, **19 A**, 381; compare Paranjape, Phalnikar and Nargund, *J. Univ. Bombay*, 1942, **11**, 124; 1943, **12**, 60.

§ *Nature*, 1944, **153**, 317.

|| *J. Amer. C.S.* 1944, **66**, 1041.

¶ *J.C.S.* 1946, p. 616.

able to exist in 16 optically active forms. Only two of these forms have so far been obtained, santonin and β -santonin (see p. 320). A certain amount of progress has, however, been made in studying the stereochemistry of the isomeric desmotropo-santonins of which, theoretically, there should be 8 optically active forms on the basis of formula (XXX). Four of these isomers have now been observed. Corresponding to the 8 optically active desmotroposantonins there should be 4 optically active santonous acids on the basis of formula (XXIX) and all these isomers have now been obtained. Theoretically hypo-



santonin, for which the formula (XII) was discussed on p. 252, should exist also in 8 optically active forms, but hyposantonin and *isohyposantonin* (see p. 289) are still the only representatives of this formula which have been isolated.

The action of acidic reagents on santanin leading to its isomerisation to *d*-desmotroposantonin has already been discussed on p. 257. When, however, santanin is treated with acidic reagents under less drastic conditions, for example with cold dilute sulphuric acid, a stereoisomer of *d*-desmotroposantonin, called

l-desmotroposantonin,* $C_{15}H_{18}O_3$, m.p. 194° , $[\alpha]_D^{28^\circ} - 140.3^\circ$ (in alcohol), *ethyl ether*, m.p. 82° , $[\alpha]_D^{27^\circ} - 129.3^\circ$ (in alcohol), *acetate*, m.p. 154° , $[\alpha]_D^{27^\circ} - 122.9^\circ$ (in alcohol), $[\alpha]_D^{24^\circ} - 119.0^\circ$ (in acetic acid) is obtained.[†] The acetate of *l*-desmotroposantonin can be prepared more conveniently by the action of acetic anhydride-sulphuric acid on santonin in the cold.[‡] When *d*-desmotroposantonin is fused with potassium hydroxide at 210 – 220° or refluxed with an alcoholic solution of sodium ethoxide a further stereoisomer, *d*-isodesmotroposantonin, m.p. 187 – 188° , $[\alpha]_D^{28^\circ} + 129.7^\circ$ (in alcohol), *methyl ether*, m.p. 111 – 112° , $[\alpha]_D^{27^\circ} + 118.2^\circ$ (in alcohol), *ethyl ether*, m.p. 82° , $[\alpha]_D^{27^\circ} + 129.6^\circ$ (in alcohol), *benzyl ether*, m.p. 82° , $[\alpha]_D^{21^\circ} + 136.5^\circ$ (in alcohol), *acetate*, m.p. 154° , $[\alpha]_D^{28^\circ} + 122.4^\circ$ (in alcohol), is produced, which is the optical enantiomorph of *l*-desmotroposantonin. On mixing these two desmotroposantonins the optically inactive racemic desmotroposantonin (see p. 265), m.p. 198° , *ethyl ether*, m.p. 106° , *acetate*, m.p. 145° , results.[§] As would be anticipated, all these desmotroposantonins afforded 1:4-dimethylnaphth-2-ol (II) (see p. 251) on fusion with potassium hydroxide at 300° .^{||} Huang-Minlon, Lo and Chu have recently described the preparation of a fourth stereoisomer of desmotroposantonin, *l*-isodesmotroposantonin, m.p. 260 – 261° , $[\alpha]_D^{20^\circ} - 106.2^\circ$ (presumably in alcohol), prepared by the action of hot diluted sulphuric acid on *d*-isodesmotroposantonin. This substance is the optical enantiomorph

* This substance is not, as its name might be taken to imply, the optical enantiomorph of *d*-desmotroposantonin but actually that of *isodesmotroposantonin*. Huang-Minlon, Lo and Chu (*J. Amer. C.S.* 1943, **65**, 1780) have proposed a more logical and systematic nomenclature for the isomeric desmotroposantonins and their derived santonous acids, but, in deference to established tradition, it has been decided to retain here the older and more familiar nomenclature.

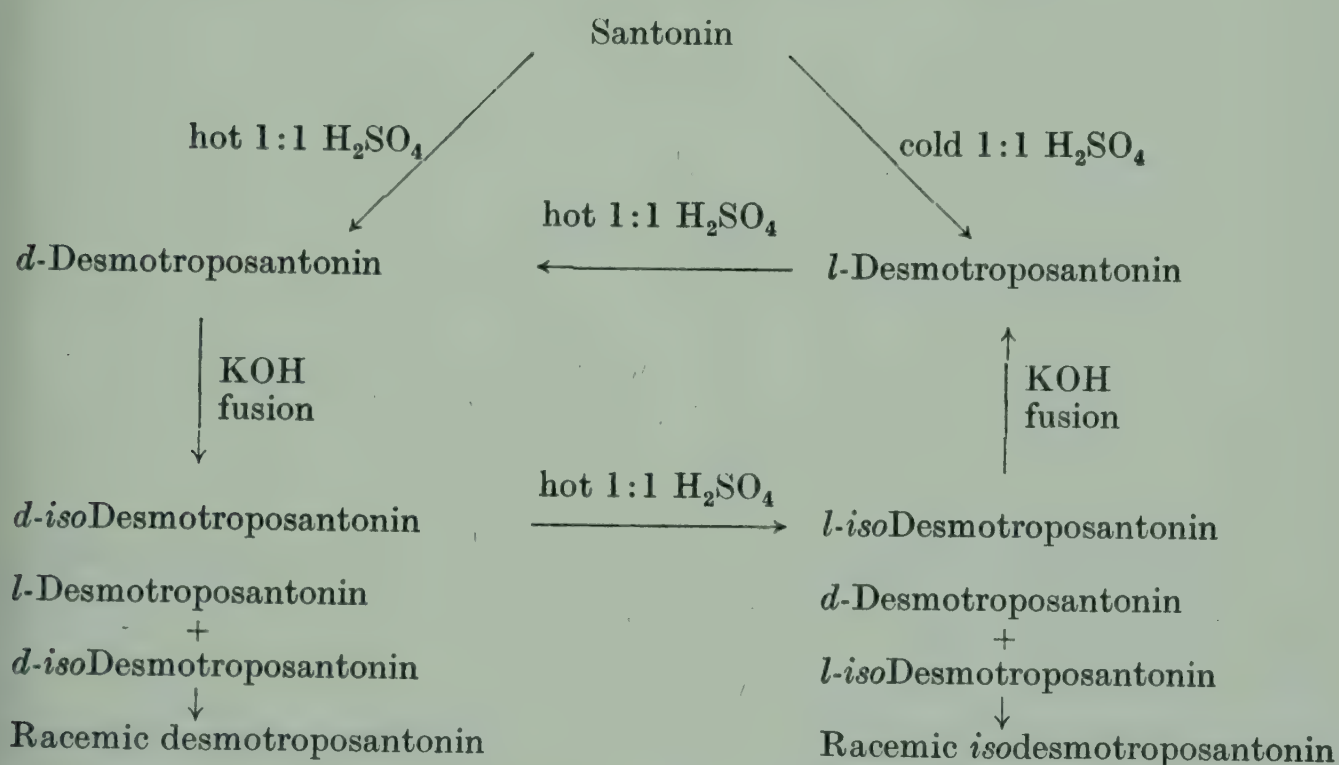
† Andreocci and Bertolo, *Ber.* 1898, **31**, 3131; *Gazz.* 1898, **28**, II, 534; *Atti R. Accad. Lincei*, 1898 [v], **7**, II, 321; Andreocci, *ibid.* 1899 [v], **8**, I, 81; *Gazz.* 1899, **29**, I, 514; Bargellini and Mannino, *Gazz.* 1909, **39**, II, 103; Bargellini and Silvestri, *ibid.* 1909, **39**, II, 347; compare Andreocci, *Gazz.* 1893, **23**, II, 469; Bertolo, *ibid.* 1899, **29**, II, 102; Bargellini, Dacanto and Mannino, *Gazz.* 1908, **38**, II, 51.

‡ Huang-Minlon, Lo and Chu, *J. Amer. C.S.* 1943, **65**, 1780.

§ Andreocci, *Gazz.* 1893, **23**, II, 484; 1895, **25**, I, 476; Castoro, *Gazz.* 1895, **25**, II, 354; compare Cannizzaro, *Ber.* 1893, **26**, 2311; Bertolo, *Gazz.* 1899, **29**, II, 102; Andreocci, *Atti R. Accad. Lincei*, 1899 [v], **8**, I, 81; *Gazz.* 1899, **29**, I, 513; Levi-Malvano and Mannino, *Atti R. Accad. Lincei*, 1908 [v], **17**, II, 487; Bargellini and Mannino, *Gazz.* 1909, **39**, II, 104; Clemo, Haworth and Walton, *J.C.S.* 1930, p. 1110.

|| Bertolo, *Atti R. Accad. Lincei*, 1902 [v], **11**, I, 490; *Gazz.* 1902, **32**, II, 374; compare the complete degradation of santonin itself under these conditions (Chiozza and Baufi, *Annalen*, 1854, **91**, 112).

of *d*-desmotroposantonin,* for the two stereoisomers afforded a new racemic *isodesmotroposantonin*, m.p. 231–232°, *acetate*, m.p. 182°, on admixture. As anticipated, racemic desmotroposantonin and racemic *isodesmotroposantonin* were interconvertible by the action of either acid or potassium hydroxide fusion. *l*-isoDesmotroposantonin, on fusion with potassium hydroxide gave its stereoisomer *l*-desmotroposantonin. These findings are contrary to the results recorded by Bargellini and Mannino,[†] who had claimed that *d*-isodesmotroposantonin was converted to the well-characterised *d*-desmotroposantonin on treatment with hot acid. However, the observations of those authors that *l*-desmotroposantonin was isomerised to *d*-desmotroposantonin by hot dilute sulphuric acid is doubtless correct (see below). The interrelationships of the four stereoisomeric desmotroposantonins can be summarised briefly in the scheme set out below.‡



It has already been mentioned on p. 251 that reduction of santonin with red phosphorus and hydriodic acid gave a mixture of *d*- and *dl*-santonous acids, which are correctly represented by the formula (XXIX) (see also p. 282). *d*-Santonous acid, C₁₅H₂₀O₃, m.p. 179–180°, $[\alpha]_D^{20} + 74.7^\circ$ (in alcohol), $+ 74.6^\circ$ (in

* Huang-Minlon, Lo and Chu now find $[\alpha]_D^{20} + 106.2^\circ$ (presumably in alcohol) for *d*-desmotroposantonin, compare p. 257.

[†] Gazz. 1909, 39, II, 103.

‡ For comment on the misleading nomenclature in common usage see p. 264, footnote *.

acetic acid), *methyl ester*, m.p. 86° , $[\alpha]_D^{18} + 84.9^{\circ}$ (in alcohol), *ethyl ester*, m.p. 117° , $[\alpha]_D^{20} + 77.9^{\circ}$ (in chloroform), $+ 72.8^{\circ}$ (in alcohol), $+ 67.3^{\circ}$ (in acetic acid), *methyl ether*, m.p. $116-117^{\circ}$, $[\alpha]_D^{27} + 72.2^{\circ}$ (in alcohol), *ethyl ether*, m.p. 120° , $[\alpha]_D^{20} + 77.9^{\circ}$ (in chloroform), $+ 74.8^{\circ}$ (in alcohol), can also be prepared by heating santonin with sulphuric or phosphoric acids, by the reduction of santonin with stannous chloride in hydrochloric acid solution, and, as is of special interest, by the reduction of *l*-desmotroposantonin with zinc dust and acetic acid.* When *d*-isodesmotroposantonin was reduced similarly with zinc dust and acetic acid it gave a stereoisomer, *l*-santonous acid, m.p. $176-177^{\circ}$, $[\alpha]_D^{28} - 74.3^{\circ}$ (in alcohol), *methyl ester*, m.p. 86° , *ethyl ester*, m.p. $116-117^{\circ}$, $[\alpha]_D^{27} - 70.6^{\circ}$ (in alcohol), *methyl ether*, m.p. $116-117^{\circ}$, *ethyl ether*, m.p. $120-121^{\circ}$, $[\alpha]_D^{15} - 73.3^{\circ}$ (in alcohol).† *l*-Santonous acid is the optical enantiomorph of *d*-santonous acid and on admixture they afford *dl*-santonous acid (see p. 257), m.p. 154° , *methyl ester*, m.p. $110.5-111^{\circ}$, *ethyl ester*, m.p. 125° , *methyl ether*, m.p. 135° , *ethyl ether*, m.p. $144-145^{\circ}$, which has been resolved to give its *d*- and *l*- components.‡ *dl*-Santonous acid can also be prepared, as would be anticipated, by the reduction of racemic desmotroposantonin (see p. 264) with zinc dust in acetic acid solution.§ The similar reduction with zinc dust of *d*-desmotroposantonin has been shown to give a further stereoisomer, *l*-desmotroposantonous acid, m.p. 175° , $[\alpha]_D^{18} - 53.3^{\circ}$ (in alcohol), *methyl ester*, m.p. $95-96^{\circ}$, $[\alpha]_D^{18} - 41.8^{\circ}$ (in alcohol), *methyl ether*, m.p. $107-108^{\circ}$, $[\alpha]_D^{28} - 49.8^{\circ}$ (in alcohol), *ethyl ether*, m.p. 127° , $[\alpha]_D - 47.2^{\circ}$ (in alcohol).|| All these isomeric santonous acids give 1:4-dimethylnaphth-2-ol (II) (see p. 251) and pro-

* Cannizzaro and Carnelutti, *Gazz.* 1873, **12**, 398; *Atti R. Accad. Lincei, Transunti*, 1879 [iii], **3**, 241; *Ber.* 1879, **12**, 1574; Andreocci, *Gazz.* 1895, **25**, **I**, 496; Andreocci and Bertolo, *Gazz.* 1898, **28**, **II**, 537; *Ber.* 1898, **31**, 3132; *Atti R. Accad. Lincei*, 1898 [v], **7**, **II**, 322; Bargellini and Silvestri, *Gazz.* 1909, **39**, **II**, 347; compare Francesconi, *Ber.* 1903, **36**, 2668; Wedekind, *ibid.* 1903, **36**, 3463.

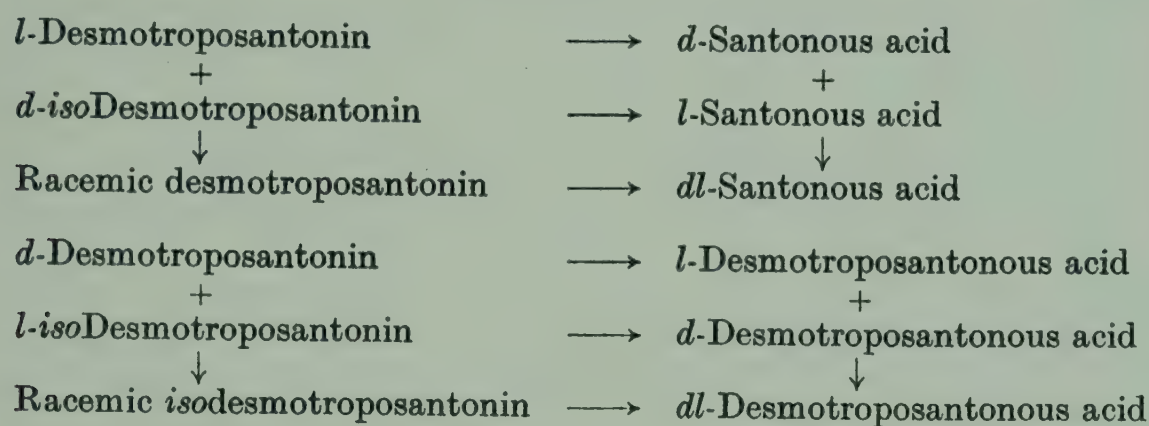
† Andreocci, *Gazz.* 1893, **23**, **II**, 488; *Atti R. Accad. Lincei*, 1895 [v], **4**, **I**, 73; *Gazz.* 1895, **25**, **I**, 516; Bertolo, *Gazz.* 1926, **56**, 859.

‡ Andreocci, *Gazz.* 1893, **23**, **II**, 489; *Atti R. Accad. Lincei*, 1895 [v], **4**, **I**, 75; *Gazz.* 1895, **25**, **I**, 526; Andreocci and Alessandrello, *Atti R. Accad. Lincei*, 1899 [v], **8**, **I**, 503; *Gazz.* 1899, **29**, **I**, 480; compare Cannizzaro and Carnelutti, *Gazz.* 1882, **12**, 400; Clemo, Haworth and Walton, *J.C.S.* 1929, p. 2368.

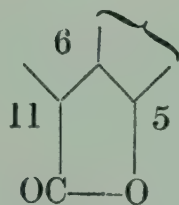
§ Andreocci and Bertolo, *Gazz.* 1898, **28**, **II**, 539; *Ber.* 1898, **31**, 3133.

|| Andreocci, *Gazz.* 1893, **23**, **II**, 477; *Ber.* 1893, **26**, 1375; Andreocci, *Gazz.* 1895, **25**, **I**, 532; *Atti R. Accad. Lincei*, 1895 [v], **4**, **I**, 75; Wedekind, *Ber.* 1898, **31**, 1677; compare Levi-Malvano and Mannino, *Atti R. Accad. Lincei*, 1908 [v], **17**, **II**, 492; 1909 [v], **18**, **II**, 147.

pionic acid on fusion with potassium hydroxide.* Huang-Minlon, Lo and Chu[†] have recently described the preparation of the fourth optically active isomer of santonous acid by the reduction with zinc dust and acetic acid of *l*-isodesmotroposantonin. This acid, *d*-desmotroposantonous acid, m.p. 175–176°, $[\alpha]_D^{21} + 54.0^\circ$ (presumably in alcohol), on admixture with *l*-desmotroposantonous acid furnished *dl*-desmotroposantonous acid, m.p. 180–181°, which could also be prepared by the reduction of racemic isodesmotroposantonin (see p. 265). The relationship of the santonous acids to the desmotroposantonins can be conveniently summarised in the following scheme.‡



Huang-Minlon[§] has reached interesting conclusions regarding the relative stereochemistry of the desmotroposantonins and the derived santonous acids. The fact that the four known desmotroposantonins can be interconverted (see p. 265) shows that during their transformations one asymmetric centre must be inverted in one reaction and the other two in the succeeding reaction. Having regard to this requirement and the nature of the reagents used, it may be assumed that alkaline fusion leads to inversion of the methyl group in the lactone ring, whilst acid treatment causes inversion at the two other asymmetric centres.



* Andreocci, *Gazz.* 1893, **23**, II, 481; *Ber.* 1893, **26**, 1375; *Gazz.* 1895, **25**, I, 544; Wedekind, *Ber.* 1898, **31**, 1677.

† *J. Amer. C.S.* 1943, **65**, 1780.

‡ For comment on the misleading nomenclature in common usage see p. 264, footnote *.

§ *J. Amer. C.S.* 1948, **70**, 611.

Now a consideration of the changes in molecular rotation accompanying these interconversions suggests that *l*-desmotroposantonin is most satisfactorily formulated as $C_5(l):C_6(d):C_{11}(d)$, where the italicised letters represent the sign of the partial rotational contribution of the asymmetric centre to the molecular rotation. The conclusions with regard to stereochemistry reached in this way are summarised in the Table.

Substance	Sign of contribution of asymmetric centre to the molecular rotation*		
	C_5	C_6	C_{11}
<i>l</i> -Desmotroposantonin	<i>l</i>	<i>d</i>	<i>d</i>
<i>d</i> -Desmotroposantonin [†]	<i>d</i>	<i>l</i>	<i>d</i>
<i>d</i> -isoDesmotroposantonin	<i>d</i>	<i>l</i>	<i>l</i>
<i>l</i> -isoDesmotroposantonin	<i>l</i>	<i>d</i>	<i>l</i>
<i>d</i> -Santonous acid	—	<i>d</i>	<i>d</i>
<i>d</i> -Desmotroposantonous acid	—	<i>d</i>	<i>l</i>

* Once the symbols *d* or *l* have been assigned to the asymmetric centres for a particular compound, then nearly all the other configurations are based on chemical arguments. The sets of configurations could, therefore, be expressed in arbitrary symbols only and relatively, one to the other, they are independent of molecular rotation arguments.

† For a comment on the misleading nomenclature in common usage see p. 264, footnote *.

Since the way in which the lactone ring is fused in these desmotroposantonins should cause a marked difference in their stabilities (the *trans* fused ring being more strained than the *cis* fused ring), it would be expected that a study of the ease of ring closure of the corresponding desmotroposantoninic acids would provide information on this point. In actual fact all the acids resemble isohyposantoninic acid in behaviour (p. 291) rather than hyposantoninic acid and it is concluded, therefore, that all four desmotroposantonins have the lactone ring *cis* fused.*

Although the ease of isomerisation of santonin to *l*-desmotroposantonin might be taken to imply that the configurations at C_5 , C_6 and C_{11} are the same in both these compounds, this is not the case. Santonin β -oxime, its acetate and the phenylhydrazone can all be transformed under very mild reducing conditions to hyposantonin (see p. 252). Santonin must, therefore, have the lactone ring fusion *trans* and be either $C_5(d):C_6(d):C_{11}(d)$ or $C_5(l):C_6(l):C_{11}(d)$. The fact that the transformation of santonin

* Huang-Minlon, *loc. cit.*; Barton, *J. Org. Chem.* 1950, 15, 466.

(*trans* fused) to the acid stable configuration of *d*-desmotropo-santonin (*cis* fused) proceeds *via l*-desmotroposantonin (also *cis* fused) proves that santonin must be $C_5(d):C_6(d):C_{11}(d)$.^{*} Since santonin is strongly laevorotatory the asymmetric centre at C_9 must be (*l*) and the large negative rotation must be due to the induced asymmetry that this centre causes in the closely neighbouring and very unsaturated dienone system.

It is mentioned on p. 320 that when β -santonin, the naturally occurring stereoisomer of santonin, is treated with acidic reagents *l*-desmotropo- β -santonin, m.p. 253° , $[\alpha]_D^{20} - 101.7^\circ$ (in ethyl acetate), is formed. By fusion with potassium hydroxide this phenol has been shown to afford *l*-desmotropo-santonin. *l*-Desmotropo- β -santonin is identical with *l*-isodesmotroposantonin[†] and, therefore, β -santonin must be $C_{11}(l)$. The change in molecular rotation on going from β -santonin ($[M]_D - 337^\circ$ in chloroform) to *l*-isodesmotroposantonin ($[M]_D - 261^\circ$ in alcohol) is $+76$ units. This is almost exactly the same as the change in molecular rotation ($+79$ units) on going from santonin ($[M]_D - 423^\circ$ in chloroform) to *l*-desmotroposantonin ($[M]_D - 344^\circ$ in alcohol), and implies a similarity in stereochemistry at C_5 , C_6 and C_9 . β -Santonin must, therefore, be $C_5(d):C_6(d):C_{11}(l):C_9(l)$.[‡]

Santonin can be characterised by its physical constants (see p. 250), by its facile conversion to *d*-desmotroposantonin (see p. 257), and by the preparation of a number of derivatives. Santonin (XXXI) affords under the usual conditions for oxime formation *santonin β -oxime* (XLVIII), $C_{15}H_{19}O_3N$, m.p. 218° , $[\alpha]_D - 80.8^\circ$ (in acetic acid), *O-benzyl ether*, m.p. $151-152^\circ$, *O-acetate*, decomp. on heating.[§] When santonin is treated with an excess of hydroxylamine it gives, besides the β -oxime mentioned above, two possibly stereoisomeric *hydroxyl-aminosantonin oximes*, $C_{15}H_{22}O_4N_2$, α -form, m.p. $229-230^\circ$ decomp., $[\alpha]_D^{12} + 47.4^\circ$ (in alcohol), *hydrochloride*, m.p. 212° decomp., *benzal* derivative, m.p. 217° decomp., β -form, m.p.

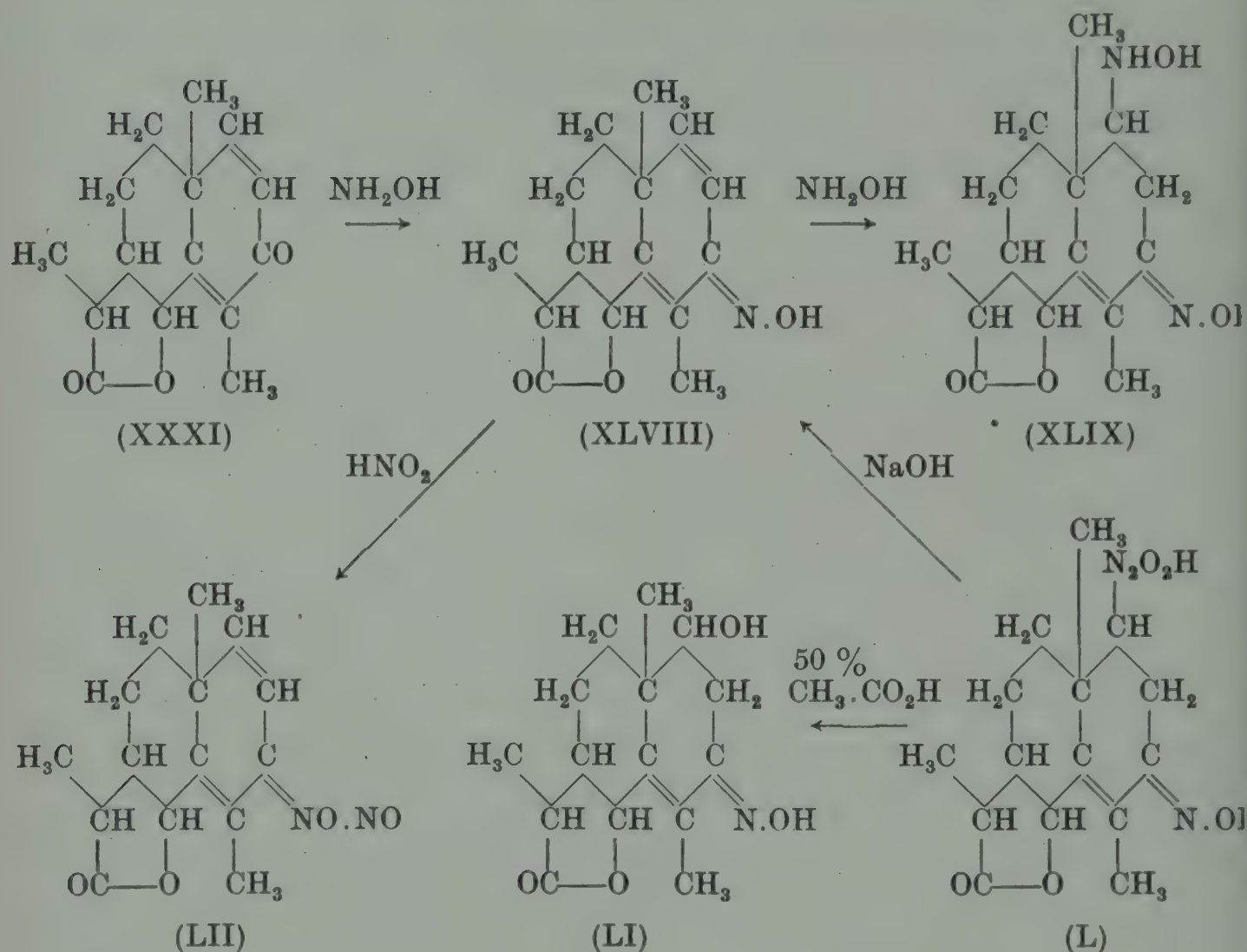
^{*} Barton, *loc. cit.*

[†] Huang-Minlon, *J. Amer. C.S.* 1948, **70**, 611.

[‡] Barton, *loc. cit.*

[§] Gucci, *Gazz.* 1889, **19**, 369; Klein, *Ber.* 1893, **26**, 411; Francesconi and Ferulli, *Gazz.* 1903, **33**, I, 196; Francesconi and Cusmano, *Atti R. Accad. Lincei*, 1908 [v], **17**, I, 67; *Gazz.* 1908, **38**, II, 56; compare Cannizzaro, *Ber.* 1885, **18**, 2746; Wedekind, *ibid.* 1899, **32**, 1413.

232–233° decomp., $[\alpha]_D^{12} - 3.0^\circ$ (in alcohol), *hydrochloride*, m.p. 163° decomp., *benzal* derivative, m.p. 140° decomp., *dibenzoyl* derivative, m.p. 184° decomp., which can probably be represented by (XLIX). These α - and β -hydroxylaminosantonin oximes furnished the corresponding stereoisomeric *nitrosohydroxylaminosantonin oximes*, $C_{15}H_{21}O_5N_3$, probably (L), α -form, m.p. 164° decomp., $[\alpha]_D^{12} - 112.8^\circ$ (in alcohol), β -form m.p. 172° decomp., respectively on treatment with nitrous acid.



By digestion with 50 per cent. acetic acid the α - and β -nitrosohydroxylaminosantonin oximes afforded two, stereoisomeric, *hydroxysantonin oximes*, $C_{15}H_{21}O_4N$, probably (LI), α -form, m.p. 199–200°, $[\alpha]_D^{12} + 219.6^\circ$ (in alcohol) and β -form, m.p. 195° decomp., $[\alpha]_D^{12} + 126.8^\circ$ (in alcohol) respectively. β -Nitrosohydroxylaminosantonin oxime, on treatment with sodium hydroxide, was reconverted to santonin β -oxime, whilst α -nitrosohydroxylaminosantonin oxime, under the same conditions, afforded the stereoisomeric *santonin α -oxime*, m.p. 230° decomp.,

hydrochloride, m.p. 168° decomp.* Both the santonin oximes reacted with nitrous acid to furnish what was probably the same *pernitrososantonin*, $C_{15}H_{18}O_4N_2$, possibly (LII), m.p. 190° decomp., $[\alpha]_D + 169.6^{\circ}$ (in chloroform), yielding *santonin semicarbazone*, m.p. 232° decomp., with semicarbazide hydrochloride and *santonin azine*, m.p. 254° decomp., with hydrazine sulphate;† *pernitrososantonin* is also said to give *isohyposantonin* (see p. 253) on reduction with sodium amalgam.‡ *Santonin phenylhydrazone* has decomp. $220-221^{\circ}$, $[\alpha]_D + 152.4^{\circ}$ (in benzene).||

A large number of colour reactions have been described for santonin; for details the original literature should be consulted.||

As might be expected in view of the pharmacological importance of santonin, numerous studies of the quantitative determination of santonin as such and of santonin in *flores cinnae* have been made for which reference should be made to the original literature.

Various addition compounds of santonin have been reported in the literature and may be used for its characterisation. With bromine and hydrobromic acid in acetic acid solution santonin gives an *addition compound*, $(C_{15}H_{18}O_3)_2 \cdot HBr, Br_2$, decomp. *ca.* 105° , which easily regenerates santonin with basic or reducing agents. The analogous *iodine compound*, $(C_{15}H_{18}O_3)_2 \cdot HI, I_2$, decomp. *ca.* 135° , is also known.¶ Addition compounds with HBr and $SnBr_4$, HCl and $SbCl_5$, and with hydroferrocyanic and hydroferricyanic acids have also been described.** With magnesium iodide santonin gives an *addition compound*, $(C_{15}H_{18}O_3)_2 \cdot MgI_2$, decomp. 175° .††

The absorption spectra in the ultra-violet of santonin and

* Francesconi and Cusmano, *Atti R. Accad. Lincei*, 1908 [v], **17**, I, 67, 211; *Gazz.* 1908, **38**, II, 55, 66; 1909, **39**, II, 111, 120; Cusmano, *Atti R. Accad. Lincei*, 1912 [v], **21**, II, 798; compare Trendelenberg, *Arch. Path.* 1916, **79**, 206.

† Francesconi and Angelucci, *Gazz.* 1901, **31**, II, 307; Francesconi and Ferulli, *ibid.* 1903, **33**, I, 196; Cusmano, *Atti R. Accad. Lincei*, 1912 [v], **21**, II, 798.

‡ Francesconi and Ferulli, *loc. cit.*

§ Grassi-Cristaldi, *Gazz.* 1887, **17**, 526; 1889, **19**, 383.

|| Trommsdorff, *Annalen*, 1834, **11**, 197; Thaeter, *Arch. Pharm.* 1897, **235**, 409; Bertolo, *Gazz.* 1899, **29**, II, 102; Wedekind, *Arch. Pharm.* 1906, **244**, 628; Reichard, *Chem. Zent.* 1907, I, 996; Ekhert, *Pharm. Zentralhalle*, 1927, **68**, 545; Woker and Antener, *Helv. Chim. Acta*, 1938, **21**, 1345.

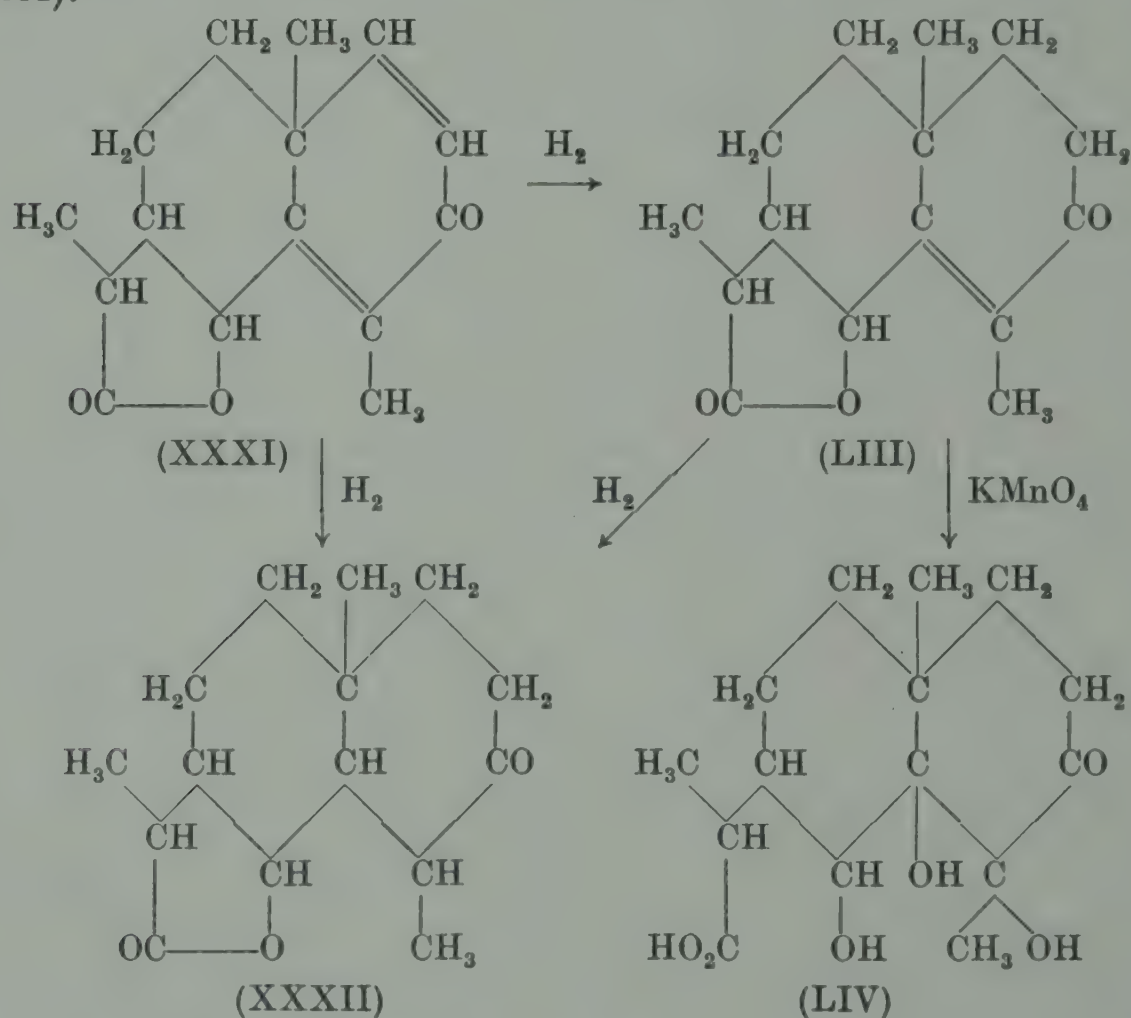
¶ Wedekind and Koch, *Ber.* 1905, **38**, 429; compare Klein, *ibid.* 1907, **40**, 939.

** Wedekind and Koch, *loc. cit.*; Wedekind, *Arch. Pharm.* 1906, **244**, 623.

†† Bowden and Watkins, *J.C.S.* 1939, p. 1961.

some of its simple derivatives have been studied by Piutti,^{*} Mayer,[†] Gomez[‡] and by Clemo and Cocker.[§] Santonin itself shows the expected $\alpha:\beta$ -unsaturated ketonic band at $236\text{ m}\mu$ ($\log \epsilon = 4.05$) and a low intensity ketonic band at $325\text{ m}\mu$ ($\log \epsilon = 1.54$).

Working with an alkaline solution Cusmano^{||} by catalytic hydrogenation was able to prepare a *dihydrosantonin*, $\text{C}_{15}\text{H}_{20}\text{O}_3$ (LIII), m.p. 105° , $[\alpha]_D^{18} + 75.3^\circ$ (in alcohol), *oxime*, m.p. 230° , $[\alpha]_D^{18} + 118^\circ$ (in methanol), *semicarbazone*, m.p. ca. 243° decomp.[¶] This substance has also been prepared by Wedekind, Goost and Jackh,^{**} who found that on further hydrogenation it afforded α -tetrahydrosantonin (XXXII),^{††} whilst on oxidation with alkaline potassium permanganate it afforded a monobasic *acid*, $\text{C}_{15}\text{H}_{24}\text{O}_6$, presumably (LIV), m.p. 198° , $[\alpha]_D^{18} + 44.8^\circ$ (in alcohol).



Atti R. Accad. Lincei, 1913 [v], **22**, II, 203.

[†] *Ibid.* 1914 [v], **23**, I, 442.

[‡] *Rev. Acad. Cienc. Madrid*, 1934, **31**, 563.

[§] *J.C.S.* 1946, p. 30.

^{||} *Atti R. Accad. Lincei*, 1913 [v], **22**, I, 508, 714; *Annalen*, 1913, **400**, 335.

The preparation of a dihydrosantonin m.p. $148\text{--}150^\circ$ was also claimed by Bargellini (*Atti R. Accad. Lincei*, 1913 [v], **22**, I, 444), but there can be little doubt that this was merely impure α -tetrahydrosantonin (compare Wedekind and Beniers, *Annalen*, 1913, **397**, 246; Wienhaus, *Ber.* 1913, **46**, 2839).

^{**} *Ber.* 1930, **63**, 50.

^{††} Compare, however, Cusmano, *loc. cit.*

By reduction of santonin with tin and hydrochloric acid Andreocci* obtained a hydrocarbon, probably 1:4-*dimethyl-7-ethylnaphthalene octahydride*, $C_{14}H_{24}$, possibly (LV), b.p. 247–248°. By the electrolytic reduction of santonin in dilute acetic acid solution Pannain† prepared a *dilactone*, $C_{30}H_{34}O_4$, m.p. 223°, $[\alpha]_D^{15} + 129.5^\circ$ (in benzene), to which the name *santonone* has been given and which is represented by (LVI). Santonone can also be prepared by the zinc dust reduction of santonin in 50 per cent. acetic acid solution, but if 70 per cent. acetic acid is used the stereoisomeric *isosantonone*, m.p. 280° decomp., $[\alpha]_D^{17} - 264.7^\circ$ (in acetic acid), is formed.‡ *isoSantonone* was also prepared by isomerisation of santonone with boiling 70 per cent. acetic acid. With barium hydroxide solution the lactone rings of santonone were opened to give *santononic acid*, $C_{30}H_{38}O_6$ (LVII), decomp. 215–216°, $[\alpha]_D^{14} + 37.1^\circ$ (in alcohol), which was reconverted to santonone with acetic anhydride, but gave *iso-santonone* with alcoholic sulphuric acid. *isoSantonone* on similar treatment with barium hydroxide solution afforded *isosantononic acid*, m.p. 167–168°, $[\alpha]_D^{20} - 40.4^\circ$ (in alcohol).§ It has been suggested|| that santonone and *isosantonone* and their respective dicarboxylic acids are related in the same way as hyposantonin and *isohyposantonin* and their respective monocarboxylic acids. If this assumption be correct then the discussion with regard to the stereochemistry of hyposantonin and *isohyposantonin* on p. 291 can be applied here also. Santonone and *isosantonone* are presumably formed by dehydration of the corresponding *pinacones*, which may be represented by (LVIII).

Both santonone and *isosantonone* gave the same *bisdihydro-santinic acid*, $C_{30}H_{34}O_4$, probably (LIX), m.p. 215°, $[\alpha]_D^{24} + 34.5^\circ$ (in acetic acid), *dimethyl ester*, m.p. 131°, $[\alpha]_D^{24} + 96.0^\circ$ (in benzene), on treatment with methanolic hydrochloric acid followed by alkaline hydrolysis.¶ This structure (LIX) for *bisdihydro-santinic acid* receives support from the oxidation experiments of Grassi-Cristaldi and Tomarchio.**

* Gazz. 1895, 25, I, 487.

† Atti R. Accad. Lincei, 1908 [v], 17, II, 499; Gazz. 1909, 39, I, 515.

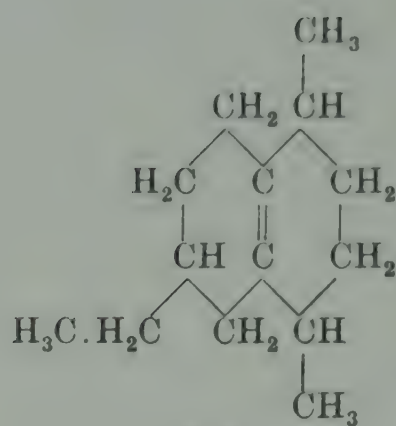
‡ Grassi-Cristaldi, Gazz. 1892, 22, II, 126.

§ Grassi-Cristaldi, loc. cit.

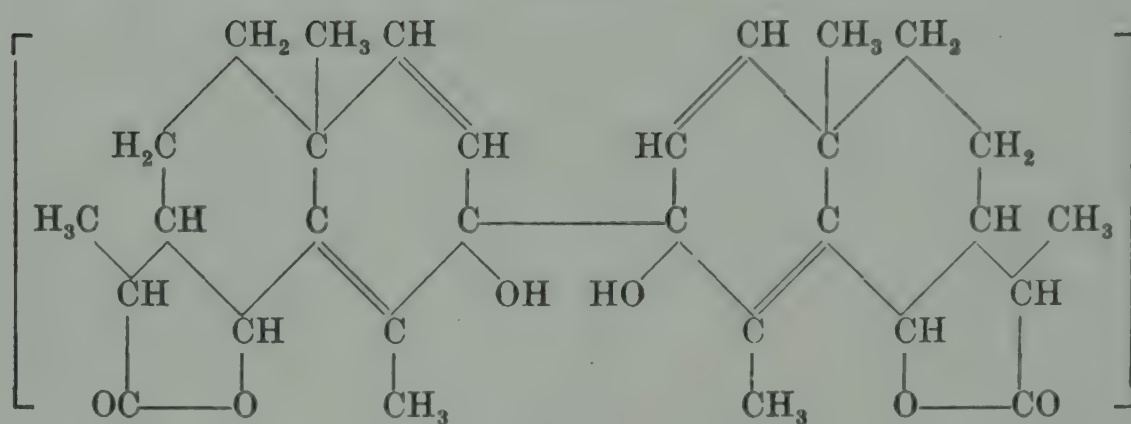
|| Grassi-Cristaldi, Gazz. 1893, 23, I, 68; compare Francesconi, Gazz. 1899, 29, II, 182.

¶ Grassi-Cristaldi, Gazz. 1893, 23, I, 60.

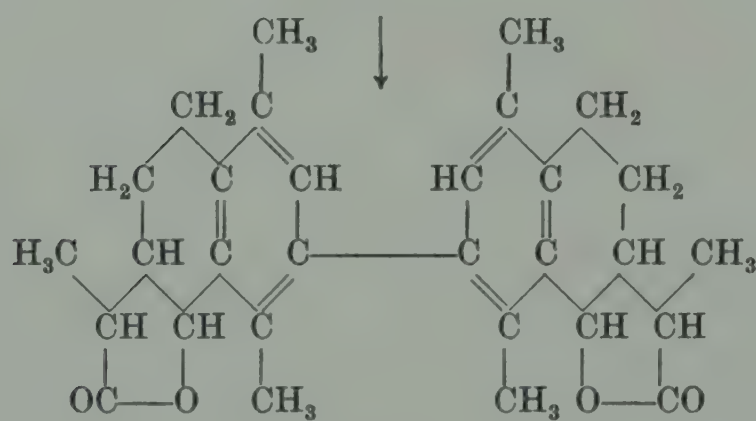
** Gazz. 1900, 30, II, 123.



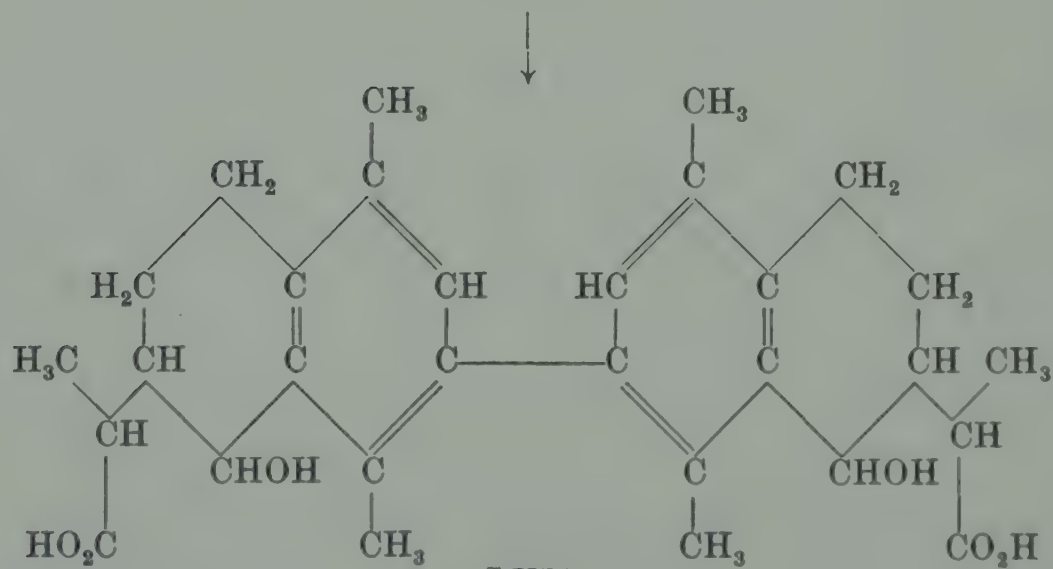
(LV)



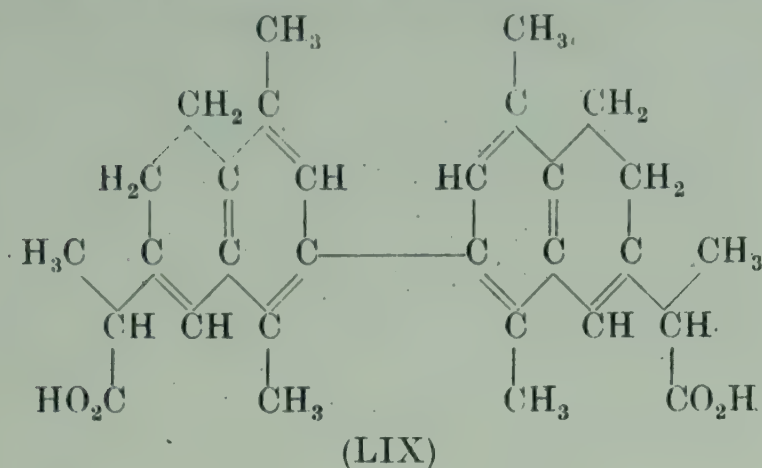
(LVIII)



(LVI)



(LVII)



Reduction of santonin with sodium amalgam has not led to the isolation of any definite products.*

When gaseous chlorine is led through a chloroform solution of santonin, *santonin dichloride*, $C_{15}H_{18}O_3Cl_2$ (LX), decomp. $173-174^\circ$, $[\alpha]_D^{15^\circ} -23^\circ$ (in alcohol), is formed.† The same compound had been prepared earlier by the addition of potassium chlorate to an alcoholic hydrochloric acid solution of santonin,‡ and by the action of chlorine on an aqueous suspension of santonin.§ By the action of aniline and alcohol or alcoholic potassium hydroxide santonin dichloride is dehydrochlorinated to give *monochlorosantonin*, $C_{15}H_{17}O_3Cl$ (LXI), m.p. 224° decomp., $[\alpha]_D^{22^\circ} -161.2^\circ$ (in alcohol).|| Wedekind and Tettweiler¶ have made a special study of these chlorinated derivatives of santonin and of their transformation products. By catalytic hydrogenation monochlorosantonin was reduced to *monochlorotetrahydrosantonin*, $C_{15}H_{21}O_3Cl$ (LXII), decomp. 215° , which could also be prepared by the chlorination of α -tetrahydrosantonin (XXXII) (see p. 276) in chloroform solution. Santonin dichloride (LX) could also be catalytically hydrogenated to give *dihydrosantonin dichloride*, $C_{15}H_{20}O_3Cl_2$ (LXIII), decomp. $145-146^\circ$, dehydrochlorinated by treatment with aniline in alcoholic solution to give *dihydromonochlorosantonin*, $C_{15}H_{19}O_3Cl$ (LXIV), decomp. 160° , which on catalytic hydrogenation afforded the same monochlorotetra-

* Cannizzaro and Sestini, *Ber.* 1873, **6**, 1201; Jaffé, *Zeit. physiol. Chem.* 1896, **22**, 550; compare Klein, *Arch. Pharm.* 1892, **230**, 504.

† Wedekind and Koch, *Ber.* 1905, **38**, 429; compare Hesse, *Annalen*, 1875, **176**, 126.

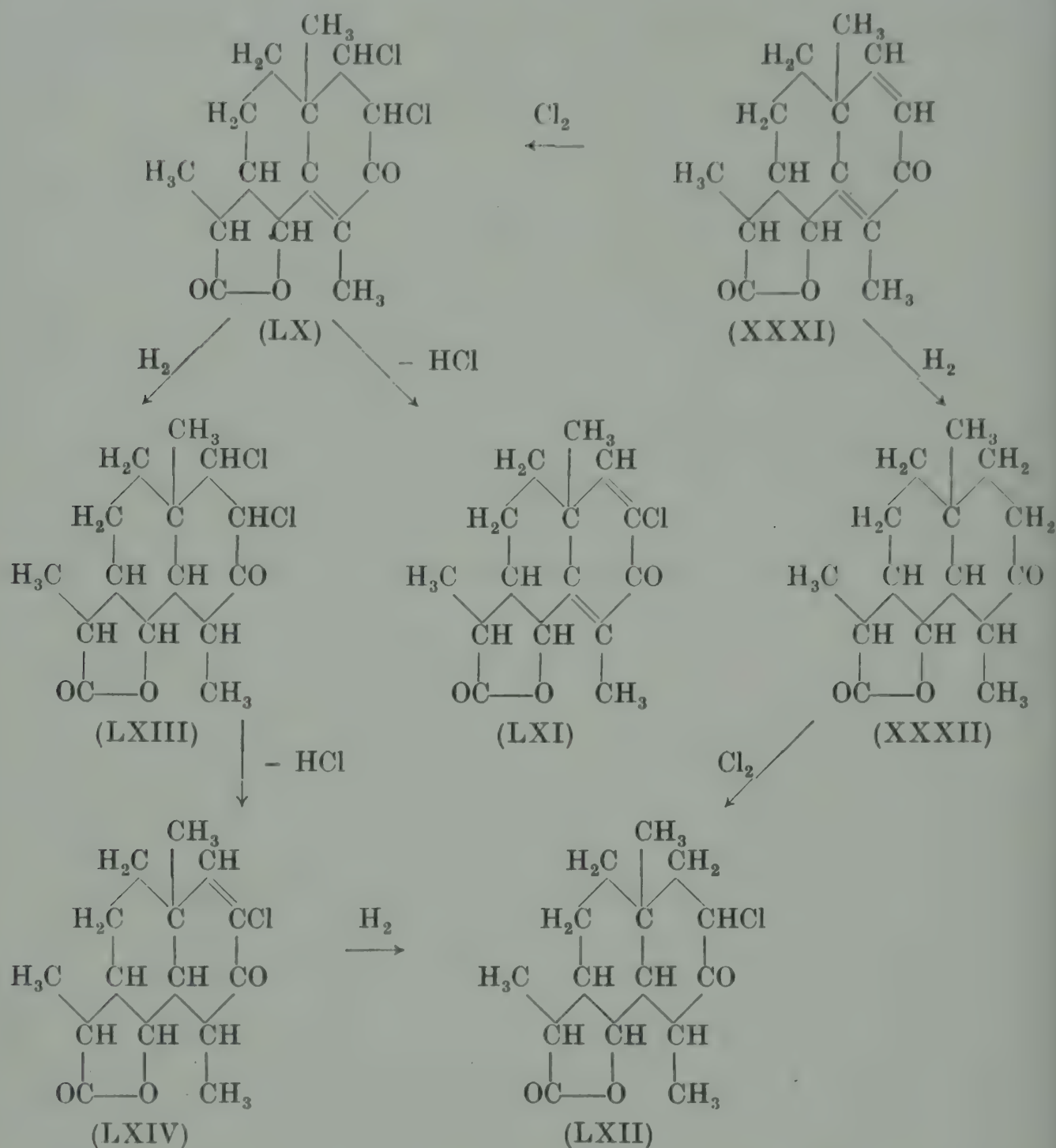
‡ Heldt, *Annalen*, 1847, **63**, 33; compare Schmidt, *Neues Jahresber. für Pharm.* **23**, 28; *Zeit. für Chem.* 1865, p. 320.

§ Sestini, *Bull. Soc. chim.* 1866 [ii], **5**, 204.

|| Wedekind and Koch, *Ber.* 1905, **38**, 429, 1848; compare Sestini, *loc. cit.*

¶ *Ber.* 1931, **64**, 387.

hydrosantonin as was prepared by the two different routes mentioned above. Francesconi and Angelucci* have described the formation of a *santonin dichloride*, m.p. 160° decomp.,



$[\alpha]_D + 230^\circ$ (in chloroform), not identical with that mentioned above. It was said to be obtained by the action of nitrosyl chloride on santonin. According to Sestini[†] a *trichlorosantonin*, C₁₅H₁₅O₃Cl₃, m.p. 213° decomp., is formed by the action of chlorine on an aqueous suspension of santonin. Santonin is said to give a *compound*, C₁₅H₁₅O₂Cl₃, decomp. 171–172°, by reaction

* Gazz. 1901, 31, II, 311.

[†] Bull. Soc. chim. 1866 [ii], 5, 202; compare Bombicci, *ibid.* 1866 [ii], 5, 204.

with phosphorus pentachloride.* The structure of neither of these trichloro-compounds is known.

When santonin is treated with chlorine water it affords, besides the compounds mentioned above, *santonin chlorohydrin*, $C_{15}H_{19}O_4Cl$ (LXV), decomp. $235-236^\circ$, as major product.† Wedekind and Tettweiler have also studied the transformation products of this substance in some detail. On catalytic hydrogenation santonin chlorohydrin furnished *dihydrosantonin chlorohydrin*, $C_{15}H_{21}O_4Cl$ (LXVI), decomp. 214° , whilst by treatment with methanolic potassium hydroxide it gave santonin α -oxide (XXXVII) (see p. 260), m.p. 214° .‡ Similarly dihydrosantonin chlorohydrin (LXVI) afforded α -dihydrosantonin α -oxide (XLVI) (see p. 262) with methanolic potassium hydroxide. When santonin α -oxide was treated with concentrated hydrochloric acid it gave a stereoisomer of (LXV), *santonin isochlorohydrin*, $C_{15}H_{19}O_4Cl$ (LXVII), decomp. 210° , which was formulated with the hydroxyl group in the *cis* configuration with respect to the chlorine atom, because it was readily reconverted to santonin α -oxide simply by boiling with aqueous pyridine. Under the same conditions this reagent did not effect conversion of santonin chlorohydrin to santonin α -oxide, so that this chlorohydrin was allotted the *trans* configuration as indicated in the formula (LXV). These views of Wedekind and Tettweiler are not in agreement with modern knowledge of the stereochemical requirements of such reactions and revision is undoubtedly necessary. On catalytic hydrogenation santonin *isochlorohydrin* (LXVII) was reduced to *dihydrosantonin isochlorohydrin*, $C_{15}H_{21}O_4Cl$ (LXVIII), decomp. 175° , which was also obtained, together with dihydrosantonin dichloride (LXIII), by the action of concentrated hydrochloric acid on α -dihydrosantonin α -oxide (XLVI). By boiling with aqueous pyridine dihydrosantonin *isochlorohydrin* furnished, as would be anticipated, α -dihydrosantonin α -oxide. Cusmano§ found that santonin β -oxide (LXIX) (see p. 260), on treatment with concentrated hydrochloric acid, afforded a *chlorohydrin*, $C_{15}H_{19}O_4Cl$, m.p. *ca.* 196° ,

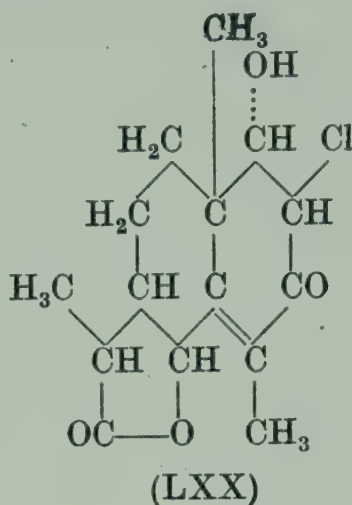
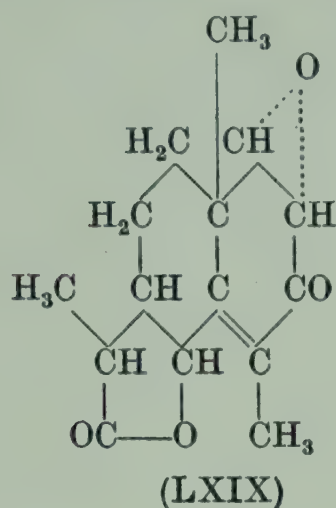
* Klein, *Ber.* 1892, **25**, 3318; 1893, **26**, 982.

† Wedekind and Koch, *Ber.* 1905, **38**, 429, 1848; compare Sestini, *loc. cit.*

‡ Santonin α -oxide is identical with the so-called δ -hydroxysantonin of Wedekind and Koch (*loc. cit.*) (see p. 260).

§ *Atti R. Accad. Lincei*, 1918 [v], **27**, 1, 118; *Gazz.* 1918, **48** 1, 248.

possibly (LXX). By treatment with zinc dust this chlorohydrin is said to regenerate santonin, whilst by boiling with alcohol it is reconverted to santonin β -oxide.



Certain bromine analogues of the chloro-compounds described above are also known. Thus the addition of bromine to an acetic acid solution of santonin leads to the formation of *santonin dibromide*, $C_{15}H_{18}O_3Br_2$ (LXXI), decomp. *ca.* 103° , which by treatment with an alcoholic aniline solution is converted to *monobromosantonin*, $C_{15}H_{17}O_3Br$ (LXXII), decomp. $212-215^\circ$, $[\alpha]_D^{20} - 137^\circ$ (in alcohol).* By the action of bromine on α -tetrahydrosantonin (XXXII), Wedekind and Beniers† obtained a *monobromotetrahydrosantonin*, $C_{15}H_{21}O_3Br$ (LXXIII), decomp. 147° , $[\alpha]_D + 9.1^\circ$ (in chloroform), whilst Wedekind and Tettweiler‡ have prepared a *santonin bromohydrin*, $C_{15}H_{19}O_4Br$, presumably (LXXIV), decomp. 216° , by the action of bromine water on santonin. This bromohydrin afforded santonin α -oxide (XXXVII) by suitable treatment with alkaline reagents.

Whilst santonin is destroyed by heating with either dilute or concentrated nitric acid§ it is said to give an *addition compound*, $C_{15}H_{18}O_3 \cdot HNO_3$, decomp. *ca.* 145° , on treatment with cold concentrated nitric acid, which regenerates santonin and nitric acid with excess of water.|| A *dinitro-compound*, $C_{15}H_{20}O_7N_2$, m.p. 187° decomp., $[\alpha]_D + 105.1^\circ$ (in alcohol), $+ 90.2^\circ$ (in chloro-

* Klein, *Ber.* 1907, **40**, 939; Wedekind, *ibid.* 1908, **41**, 359; compare Klein, *ibid.* 1892, **25**, 3317; Wedekind, *Arch. Pharm.* 1906, **244**, 627.

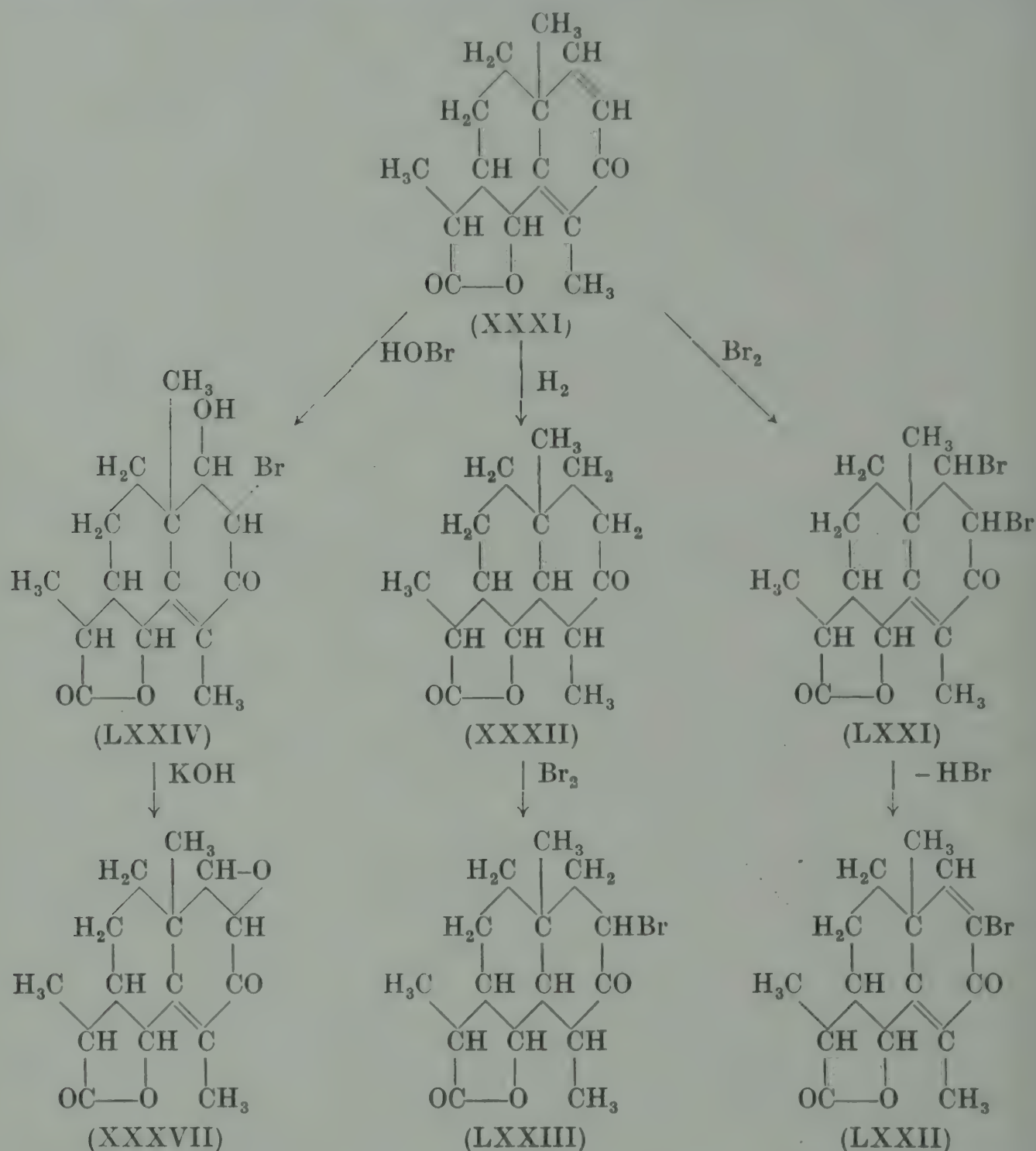
† *Annalen*, 1913, **397**, 246.

‡ *Ber.* 1931, **64**, 387.

§ Trommsdorff, *Annalen*, 1934, **11**, 195; Heldt, *ibid.* 1847, **63**, 41; Wagner, *Ber.* 1887, **20**, 1663.

|| Andreocci, *Atti R. Accad. Lincei*, 1896 [v], **5**, II, 309; Wedekind and Koch, *Ber.* 1905, **38**, 429.

form), has been prepared by the action of concentrated nitric acid on α -tetrahydrosantonin.*



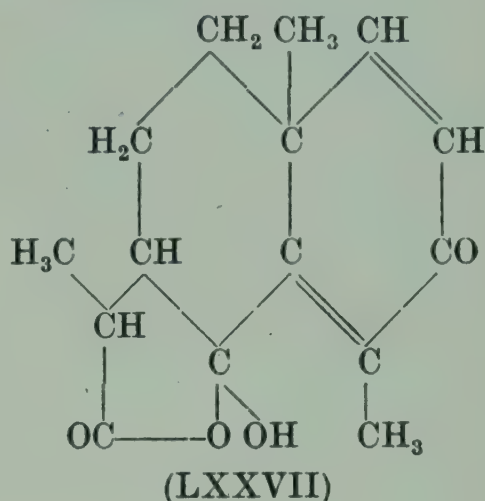
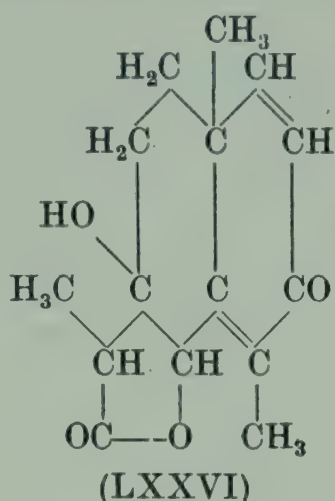
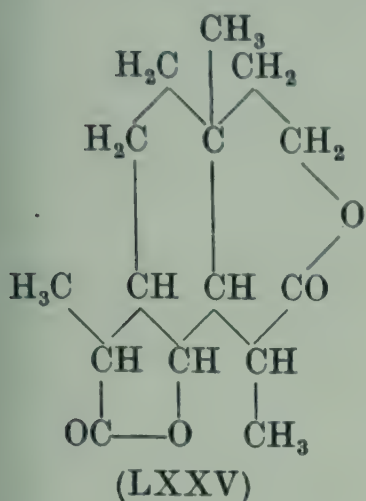
When α -tetrahydrosantonin is oxidised with Caro's acid it gives α -tetrahydrosantonilide, $\text{C}_{15}\text{H}_{22}\text{O}_4$ (LXXV), m.p. 159.5° , $[\alpha]_D -47.2^\circ$ (in benzene), -31.2° (in chloroform), -35.1° (in alcohol). As would be expected santonin itself does not give a comparable reaction.†

When treated with liquid ammonia the lactone ring of santonin is opened with formation of *santoninic acid amide*,

* Wedekind and Beniers, *Annalen*, 1913, **397**, 246.

† Wedekind, *Ber.* 1914, **47**, 2483.

$C_{15}H_{21}O_3N$, m.p. 177° , $[\alpha]_D^{23} - 15.3^\circ$ (in alcohol).^{*} The kinetics of this reaction have been studied in some detail.[†]



Santonin is metabolised by the dog with oxidation and subsequent excretion in the urine of α -hydroxysantonin, $C_{15}H_{18}O_4$, m.p. 286° , $[\alpha]_D^{20} - 133.9^\circ$ or *ca.* -115° (in alcohol), *acetate*, m.p. 173° , *phenylhydrazone*, m.p. $264-265^\circ$ decomp., and β -hydroxysantonin, $C_{15}H_{18}O_4$, m.p. $128-131^\circ$.[‡] Beyond mention of its isolation β -hydroxysantonin has not been studied further; α -hydroxysantonin, on the other hand, has been examined fairly thoroughly by Asahina and Momose.[§]

α -Hydroxysantonin differs from santonin in that it has an additional hydroxyl group, which must be tertiary because of its sterically protected character. By treatment with formic acid or hydrochloric acid it gave an unsaturated phenolic *lactone*, $C_{15}H_{16}O_3$, m.p. $244-246^\circ$, *methyl ether*, m.p. $165-166^\circ$, *acetate*, m.p. 183° . By the action of alkali this phenolic lactone was transformed into a ketonic *acid*, $C_{15}H_{18}O_4$, m.p. $192-193^\circ$, *methyl ester*, m.p. 138° , *enol acetate*, m.p. 183° , whilst on reduction with sodium amalgam it gave racemic desmotroposantonin (XXX) (see pp. 263-8), and on catalytic hydrogenation with a palladised charcoal catalyst in acetic acid solution it afforded *dl*-santonous acid (XXIX) (see pp. 266-8). Asahina and Momose suggested, on the basis of these reactions, that α -hydroxysantonin should be represented by (LXXVI). This formula is identical with that

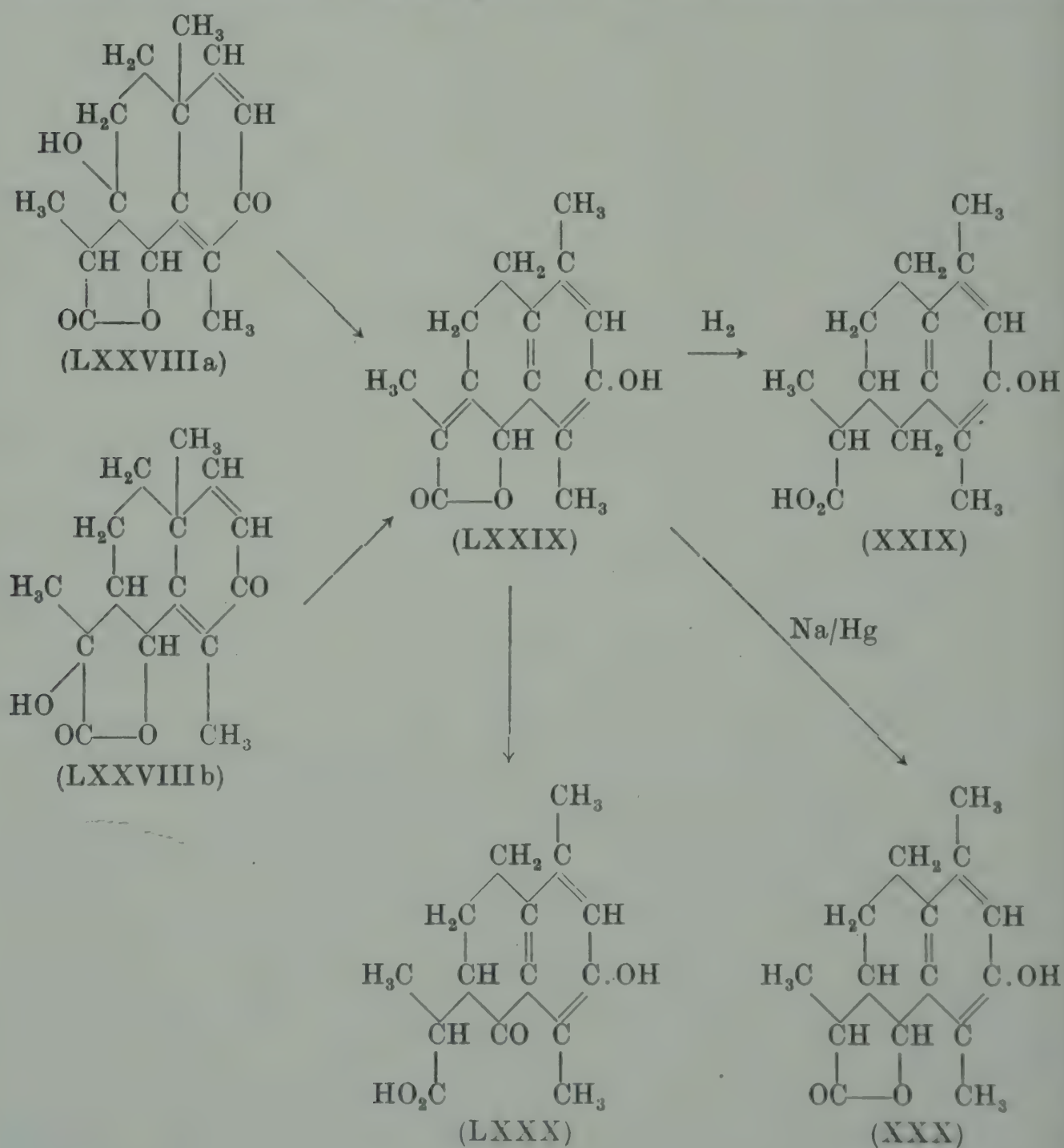
^{*} Josephson, *Svensk. Farm. Tids.* 1931, **35**, 29, 69; Abkin and Medvedev, *J. Gen. Chem. U.S.S.R.* 1934, **4**, 1407.

[†] Shatenshtein, *inter. al. J. Phys. Chem. U.S.S.R.* 1936, **8**, 613; *J. Amer. C.S.* 1937, **59**, 432.

[‡] Jaffé, *Zeit. Physiol. Chem.* 1897, **22**, 553; Lo Monaco, *Gazz.* 1897, **27**, II, 87.

[§] *Ber.* 1937, **70**, 812.

accepted on p. 312 for artemisin and the Japanese workers, realising this, further suggested that the formula for artemisin should be modified to (LXXVII). In view of the strong evidence which has been obtained in support of the formula assigned to artemisin these criticisms cannot be accepted and α -hydroxy-santonin must be either a stereoisomer of artemisin (LXXVIIIa) or be represented by (LXXVIIIb). It is not possible to distinguish between these two formulae on the basis of the evidence at present available. Formula (LXXVIII) explains readily the formation of *dl*-santonous acid by the reduction of the phenolic lactone, $C_{15}H_{16}O_3$, now formulated as (LXXIX). It also explains the reduction to racemic desmotroposantonin and the formation of the ketonic acid, $C_{15}H_{18}O_4$ (LXXX), for under the influence of



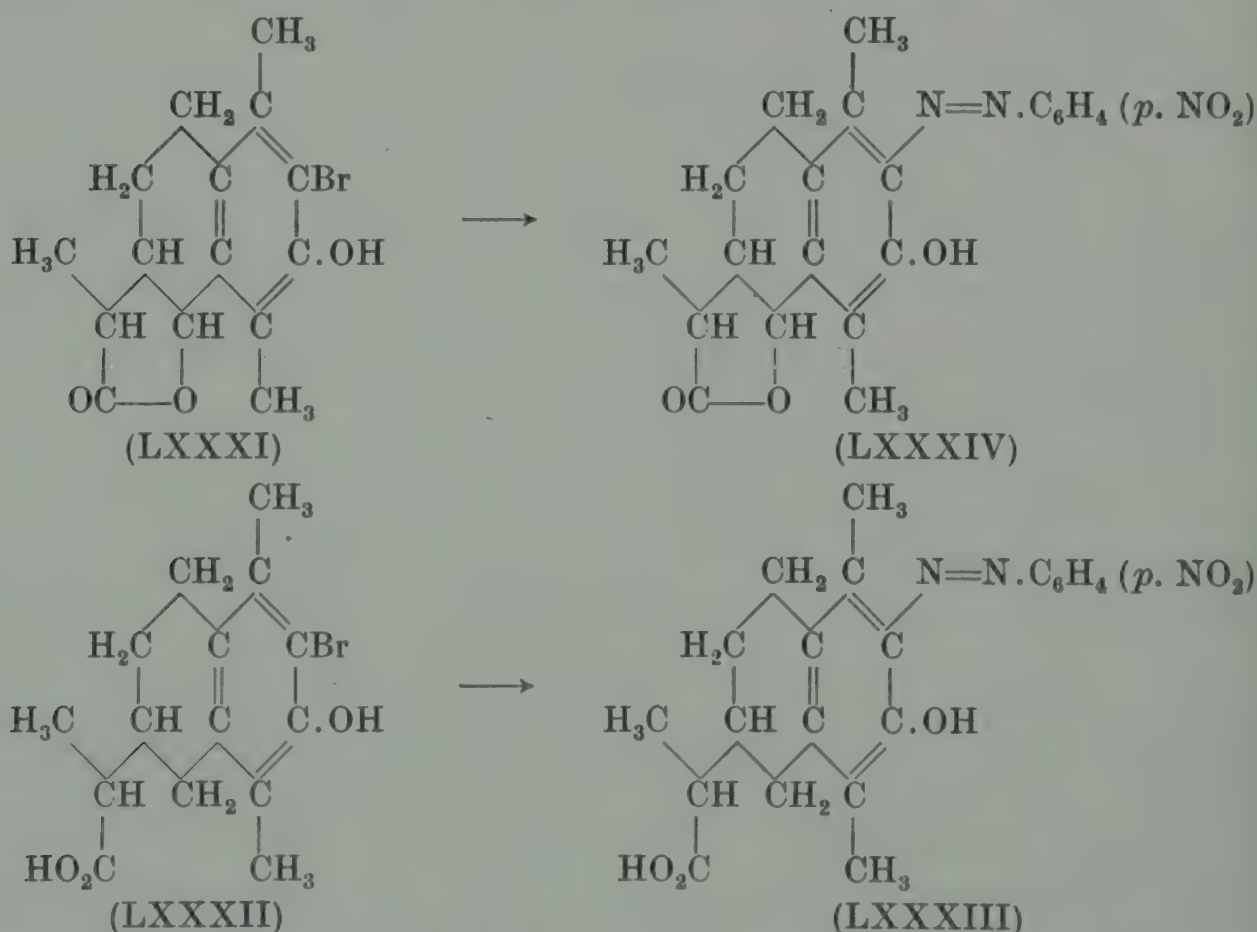
the alkaline reagents used to effect these transformations the double bond, $\alpha:\beta$ - with respect to the carbonyl group, must be in a state of tautomeric mobility. The prolonged action of alkali on α -hydroxysantonin is discussed on p. 302.

Huang-Minlon, Lo and Chu* have studied the formation and properties of the monobromodesmotroposantonins, $C_{15}H_{17}O_3Br$ (LXXXI). Monobromosantonin (p. 279) on treatment with acetic anhydride-sulphuric acid mixture afforded *monobromo-l-desmotroposantonin*, m.p. 121–123°, *acetate*, m.p. 182–183°, also prepared by direct bromination of *l*-desmotroposantonin. Direct bromination of *d*-desmotroposantonin and of *d*-isodesmotroposantonin furnished the corresponding *monobromo-compounds*, m.p.s 210–211° and 121–122° respectively. The latter compound was also prepared by the fusion of the monobromo-*d*-desmotroposantonin with potassium hydroxide. In a similar manner direct bromination of *l*-isodesmotroposantonin gave the corresponding *monobromo-compound*, m.p. 210–211°, which by fusion with potassium hydroxide, was converted, as expected, to the monobromo-*l*-desmotroposantonin mentioned above. Direct bromination of *dl*-desmotroposantonin furnished *monobromo-dl-desmotroposantonin*, m.p. 188–189°, which was also obtained by suitable admixture of monobromo-*l*-desmotroposantonin and monobromo-*d*-isodesmotroposantonin. Likewise direct bromination of *dl*-isodesmotroposantonin gave *monobromo-dl-isodesmotroposantonin*, m.p. 203–204°, also prepared by suitable admixture of monobromo-*d*-desmotroposantonin and monobromo-*l*-isodesmotroposantonin. Huang-Minlon, Lo and Chu have also studied some of the related monobromosantonous acids, $C_{15}H_{19}O_3Br$ (LXXXII) (p. 284). By direct bromination *d*-santonous acid was converted to *monobromo-d-santonous acid*, m.p. 116–118°, $[\alpha]_D^{14} + 69.7^\circ$ (in alcohol), *ethyl ester*, m.p. 86°, $[\alpha]_D^{15} + 68.2^\circ$ (in alcohol), which had been prepared previously by bromination of ethyl *d*-santonite.[†] *l*-Desmotroposantonous acid was similarly brominated to give *monobromo-l-desmotroposantonous acid*, m.p. 120–122°,

* *J. Amer. C.S.* 1944, **66**, 1954.

[†] Andreocci, *Gazz.* 1895, **25**, **1**, 501, 547; *Atti R. Accad. Lincei*, 1895 [v], **4**, **1**, 76; Andreocci has also described a so-called β -form of this acid, m.p. 159–160°, $[\alpha]_D^{14} + 61.9^\circ$ (in alcohol), said to be obtained if ethyl monobromo-*d*-santonite is hydrolysed with hot alkali instead of in the cold.

which had previously been prepared by Andreocci.* Andreocci has also described the preparation of *monobromo-l-santonous acid*, m.p. 116°, $[\alpha]_D^{15} - 69.4^\circ$ (in alcohol), *ethyl ester*, m.p. 86°, $[\alpha]_D^{15} - 68.5^\circ$ (in alcohol) and *monobromo-dl-santonous acid*, m.p. 193–195°, *ethyl ester*, m.p. 104–106°, the former being obtained by bromination of ethyl *l*-santonite and the latter by suitable admixture of monobromo-*d*-santonous acid and monobromo-*l*-santonous acid. On fusing monobromo-*d*-santonous acid with potassium hydroxide Andreocci observed the formation of 1:4-dimethylnaphth-2-ol, propionic acid and hydrobromic acid, as would be anticipated. Huang-Minlon, Lo and Chu found that when monobromo-*d*-santonous acid was treated with diazotised *p*-nitraniline it gave an *azo-compound* (LXXXIII), m.p. 214–215°, which was also obtained by coupling *d*-santonous acid with the same reagent. In a similar manner monobromo-*d*-desmotroposantonin reacted with diazotised *p*-nitraniline to give an *azo-compound* (LXXXIV), m.p. 259–260°.† Wedekind‡ has made

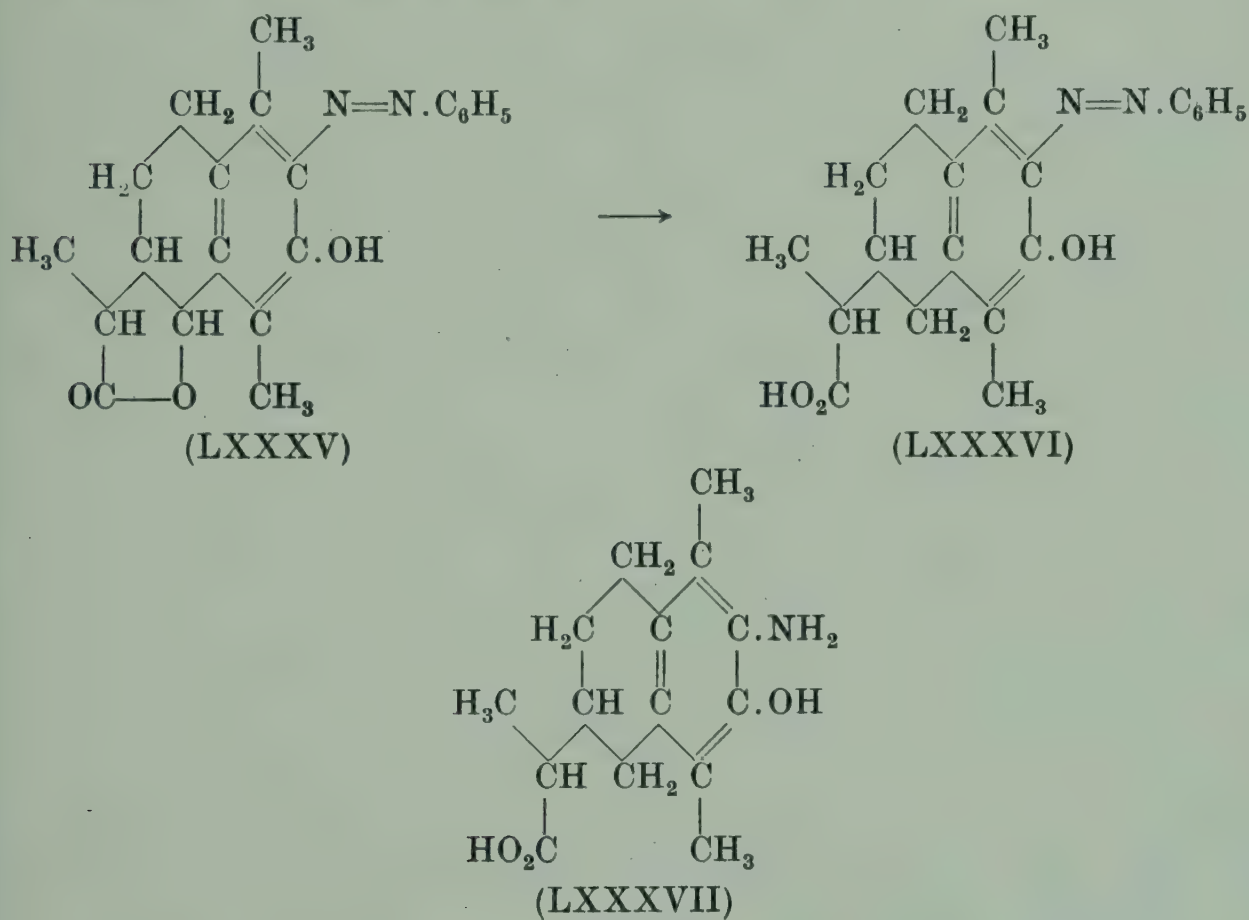


* *Loc. cit.*; compare *Gazz.* 1893, 23, II, 480. Andreocci, however, recorded m.p. 92°, $[\alpha]_D^{15} - 50.4^\circ$ (in alcohol) for this substance.

† Huang-Minlon, Lo and Chu state (*loc. cit.*) that this compound was prepared prior to their experiments by Wedekind and Koch and quote *Ber.* 1903, 36, 1391. No such compound, however, is described in this paper and, indeed, it does not appear to be mentioned in the literature prior to the work of the Chinese authors.

‡ Wedekind and Schmidt, *loc. cit.*; *Compt. rend.* 1902, 135, 44; Wedekind, *Zeit. Physiol. Chem.* 1904, 43, 241; *Chem. Zent.* 1905, I, 1025.

a special study of the coupling of diazotised aromatic amines with *d*-santonous acid, *l*-desmotroposantonous acid and *d*-desmotroposantonin, but only a few of the compounds formed call for special mention here. Diazotised aniline coupled with *d*-desmotroposantonin to give the *benzeneazo-derivative*, $C_{21}H_{22}O_3N_2$ (LXXXV), m.p. 260° , which by reduction with zinc dust and acetic acid furnished *benzeneazo-l-desmotroposantonous acid*, $C_{21}H_{24}O_3N_2$ (LXXXVI), m.p. 218° decomp., and by reduction with stannous chloride in hydrochloric acid solution afforded *amino-l-desmotroposantonous acid*, $C_{15}H_{21}O_3N$ (LXXXVII), m.p. 206° . For details of the other azo compounds prepared by Wedekind, the original literature should be consulted.



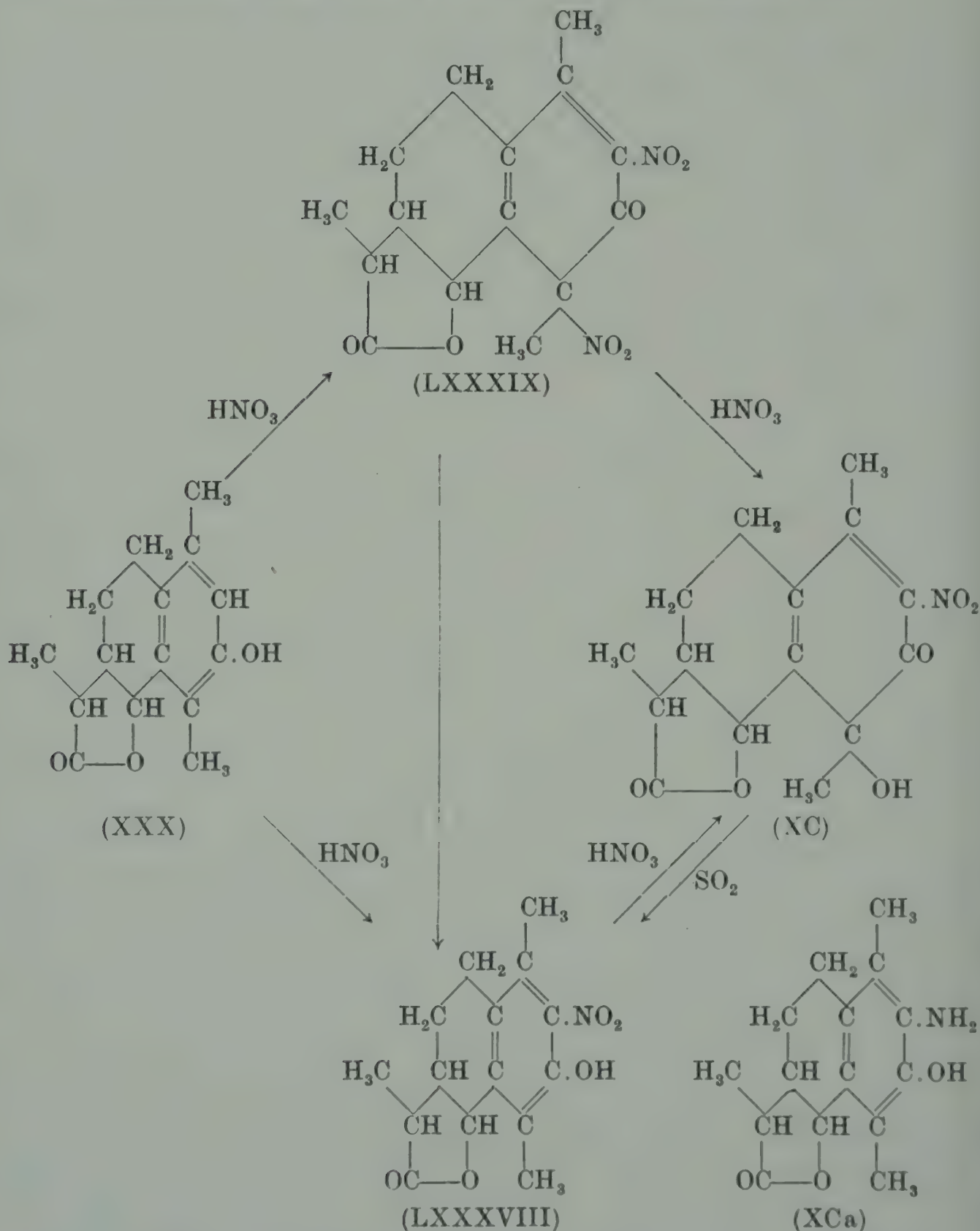
The action of nitric acid on *d*-desmotroposantonin (XXX), has been studied by Andreocci,* Bargellini† and Bargellini and Daconto.‡ Depending upon the conditions used *mononitro-d-desmotroposantonin*, $C_{15}H_{17}O_5N$ (LXXXVIII), m.p. 191° decomp., $[\alpha]_D^{24} + 115.4^\circ$ (in alcohol), *acetate*, m.p. $166-167^\circ$ $[\alpha]_D^{23} + 111.8^\circ$ (in alcohol), or a *compound*, $C_{15}H_{16}O_7N_2$, m.p. *ca.* 120° decomp., formulated as (LXXXIX), are obtained. The latter compound by digestion with alkali or methyl alcohol

* *Atti R. Accad. Lincei*, 1896 [v], 5, II, 312; *Chem. Zent.* 1897, I, 169.

† *Atti R. Accad. Lincei*, 1907 [v], 16, II, 263; *Gazz.* 1907, 37, II, 417.

‡ *Gazz.* 1908, 38, II, 42.

afforded (LXXXVIII), whilst by further treatment with nitric acid it furnished a *substance*, $C_{15}H_{17}O_6N$, decomp. $237-240^\circ$, *acetate* m.p. $186-188^\circ$, formulated as (XC), which was also obtained by the further action of nitric acid on (LXXXVIII), and which was reconverted to the mononitro-*d*-desmotroposantonin by prolonged reduction with sulphurous acid. *l*-Desmotroposantonin is said to give the corresponding *analogue* of (XC), decomp. $218-220^\circ$, by treatment with nitric acid.*



* Bargellini, Daconto and Mannino, *Gazz.* 1908, **38**, II, 51.

Recently Huang-Minlon and Cheng* have studied the nitration of *d*- and *l*-desmotroposantonins in some detail and have investigated the action of various reducing agents on the nitrated products. *d*-Desmotroposantonin afforded the nitro derivative mentioned above whilst *l*-desmotroposantonin, using the same mild nitration procedure, gave *mononitro-l-desmotroposantonin*, $C_{15}H_{17}O_5N$, m.p. 216–217°, $[\alpha]_D^{25^\circ} - 105^\circ$ (in alcohol). Mild reduction of mononitro-*d*-desmotroposantonin furnished *amino-d-desmotroposantonin*, $C_{15}H_{19}O_3N$ (XCa), m.p. 197–198°, $[\alpha]_D^{23^\circ} + 113.8^\circ$ (in alcohol), *hydrochloride*, m.p. 265–267° decomp., $[\alpha]_D^{25^\circ} + 66.4^\circ$ (in alcohol), whilst more drastic conditions gave an *amino-l-desmotroposantonous acid*, $C_{15}H_{21}O_3N$, m.p. 190°, $[\alpha]_D^{25^\circ} - 56.3^\circ$ (in alcohol), *hydrochloride*, m.p. 245–246° decomp., $[\alpha]_D^{24^\circ} - 59.2^\circ$ (in alcohol), apparently not identical with the amino-*l*-desmotroposantonous acid m.p. 206° of Wedekind (see above). Similarly mononitro-*l*-desmotroposantonin afforded *amino-l-desmotroposantonin*, $C_{15}H_{19}O_3N$, m.p. 170°, $[\alpha]_D^{25^\circ} - 157.5^\circ$ (in alcohol), *hydrochloride*, m.p. 273–274°, $[\alpha]_D^{25^\circ} - 125^\circ$ (in alcohol) and *amino-d-desmotroposantonous acid*, $C_{15}H_{21}O_3N$, m.p. 197°, $[\alpha]_D^{25^\circ} + 76.2^\circ$ (in alcohol). As would be expected application of the Sandmeyer reaction to amino-*d*-desmotroposantonin gave the monobromo-*d*-desmotroposantonin previously mentioned on p. 283.

The stereoisomeric *desmotroposantoninic acids* (XCI), like santoninic acid (see p. 250), are obtained by the action of alkali on the desmotroposantonins. They are unstable and have received little attention.†

When *d*-desmotroposantonin or santonin are digested with hydrochloric acid containing dissolved zinc chloride they furnish an *acid*, $C_{15}H_{18}O_3$, m.p. 97–98°, *ethyl ester*, m.p. 74–75°, *ethyl ester acetate*, m.p. 72°, *ethyl ester ethyl ether*, m.p. 68–70°, which Bertolo‡ has called *dihydroartemisic acid* because of its relationship to artemisic acid.§ In view of the lack of optical activity in this substance it should doubtless be formulated as (XCII). On fusion with potassium hydroxide dihydroartemisic acid

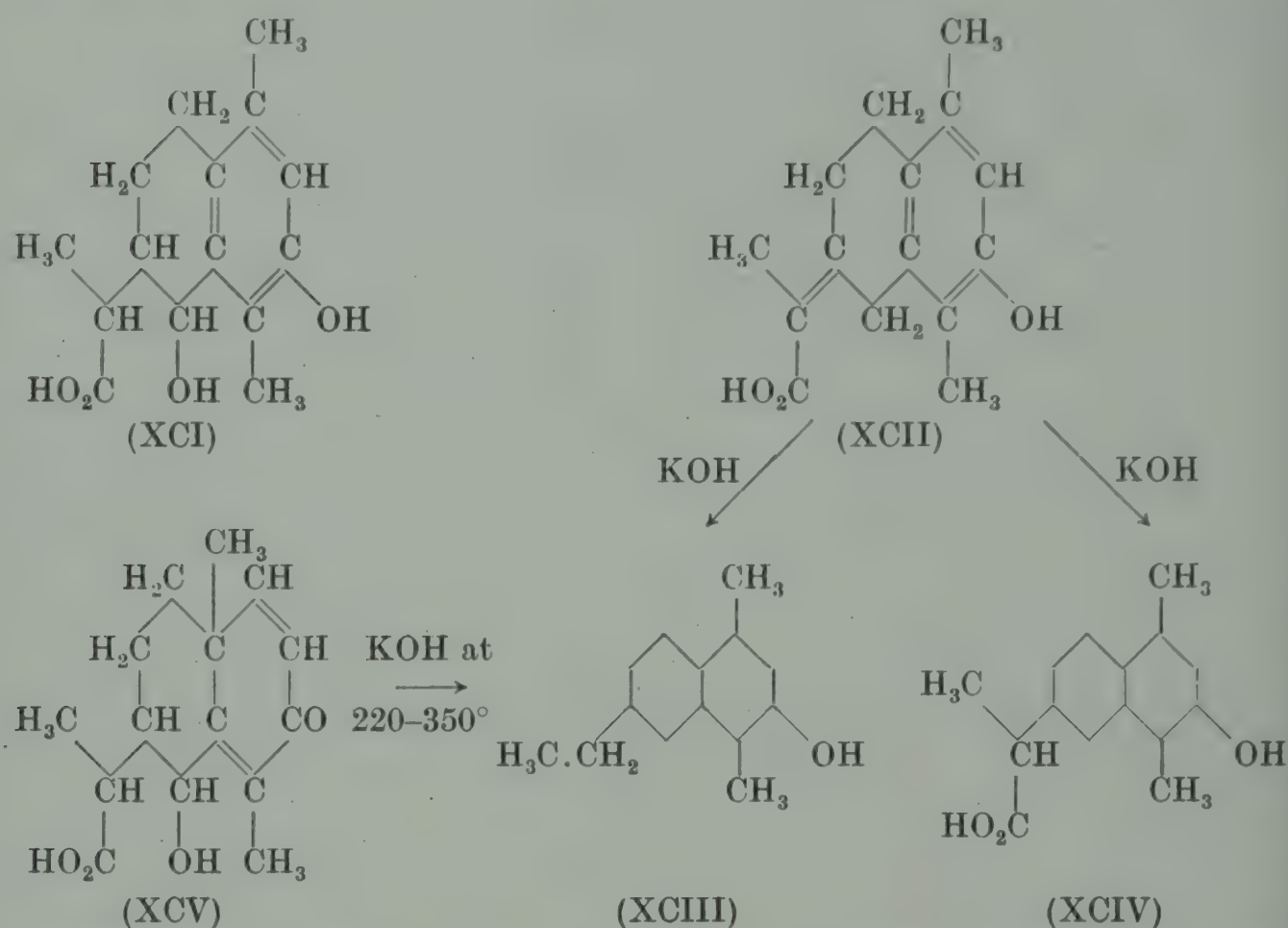
* *J. Amer. C.S.* 1948, **70**, 449.

† Andreocci, *Gazz.* 1893, **23**, II, 476; Andreocci and Bertolo, *Atti R. Accad. Lincei*, 1898 [v], **7**, II, 322; *Gazz.* 1898, **28**, II, 535.

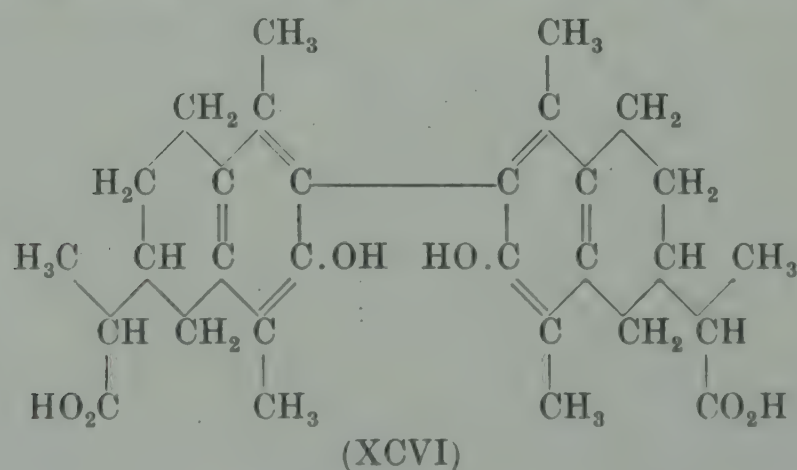
‡ *Gazz.* 1926, **56**, 852; *Atti IV Congr. naz. chim. pura applicata* (1932), 1933, p. 396.

§ It is suggested that a more suitable name for this substance would be *dihydrohyposantinic acid*, compare p. 253.

afforded 1:4-dimethyl-7-ethylnaphth-2-ol (XCIII), $C_{14}H_{16}O$, m.p. 126° , methyl ether, m.p. 72° , and some artemisic acid (XCIV). Bertolo* also obtained the same naphthol (XCIII) by fusing santoninic acid (XCV) with potassium hydroxide at $220-350^{\circ}$.



When any of the santonous or desmotroposantonous acids (see pp. 265, 266) are treated with ferric chloride they afford dimeric products, $C_{30}H_{38}O_6$, represented by the formula (XCVI). *d*-Disantonous acid has m.p. $250-250.5^{\circ}$ decomp., $[\alpha]_D^{21} + 85.9^{\circ}$ (in alcohol), diethyl ester, m.p. 183° , whilst *l*-disantonous acid has m.p. $250-250.5^{\circ}$ decomp., $[\alpha]_D^{21} - 85.8^{\circ}$ (in



* Gazz. 1926, 56, 856.

alcohol). On suitable admixture these two acids give *dl-di-santonous acid*, m.p. 243–244° decomp.,* also obtained from *dl-santonous acid* by the action of ferric chloride. *l-Didesmotroposantonous acid* has m.p. 254–255°, $[\alpha]_D^{21} - 64.5^\circ$ (in alcohol).†

The formation of the stereoisomeric hyposantonin and *iso*-hyposantonin and some of their transformation products has already been briefly discussed on pp. 253, 263. Asahina and Momose‡ have examined in some detail the chemistry of *iso*-hyposantonin. When hyposantonin, for which the formula (XII) (see p. 253) is still correct, was nitrated with nitric acid-acetic acid mixture it furnished *mononitroisohyposantonin*,§ $C_{15}H_{17}O_4N$ (XCVII), m.p. 183°, $[\alpha]_D^{24} - 67.6^\circ$ (in chloroform), reduced by zinc dust in ammonium chloride solution to *aminoisohyposantonin*, $C_{15}H_{19}O_2N$ (XCVIII), m.p. 193°, $[\alpha]_D^{24} - 165.7^\circ$, *hydrochloride*, m.p. 118–119° decomp., and by catalytic hydrogenation with a palladised charcoal catalyst in alcoholic solution to *amino-d-santonous acid*, $C_{15}H_{21}O_2N$ (XCIX), m.p. 246°, *hydrochloride*, m.p. 212–213° decomp., $[\alpha]_D^{23} + 62.5^\circ$ (in 1 per cent. hydrochloric acid solution). *Aminoisohyposantonin* on treatment with nitrous acid afforded *l-desmotroposantonin* (XXX), whilst *amino-d-santonous acid* with the same reagent gave *d-santonous acid* (XXIX). On further nitration with nitric acid-sulphuric acid mixture *mononitroisohyposantonin* (XCVII) furnished *dinitroisohyposantonin*, $C_{15}H_{16}O_6N_2$ (C), m.p. 209°, $[\alpha]_D^{22} - 62.0^\circ$ (in chloroform), reduced by catalytic hydrogenation with a palladised charcoal catalyst to *diamino-d-santonous acid*, $C_{15}H_{20}O_2N_2$ (CI), m.p. 218–219°, $[\alpha]_D^{25} + 79.1^\circ$ (in 1 per cent. hydrochloric acid solution). By oxidation with Caro's acid *aminoisohyposantonin* (XCVIII) was converted to *nitrosohyposantonin*, $C_{15}H_{17}O_3N$ (CII), m.p. 146° decomp., $[\alpha]_D^{18} - 185.8^\circ$ (in chloroform), which by reduction with sodium sulphite gave what was presumably the corresponding *hydroxylamine* (CIII). This hydroxylamine was not, however, isolated but by treatment

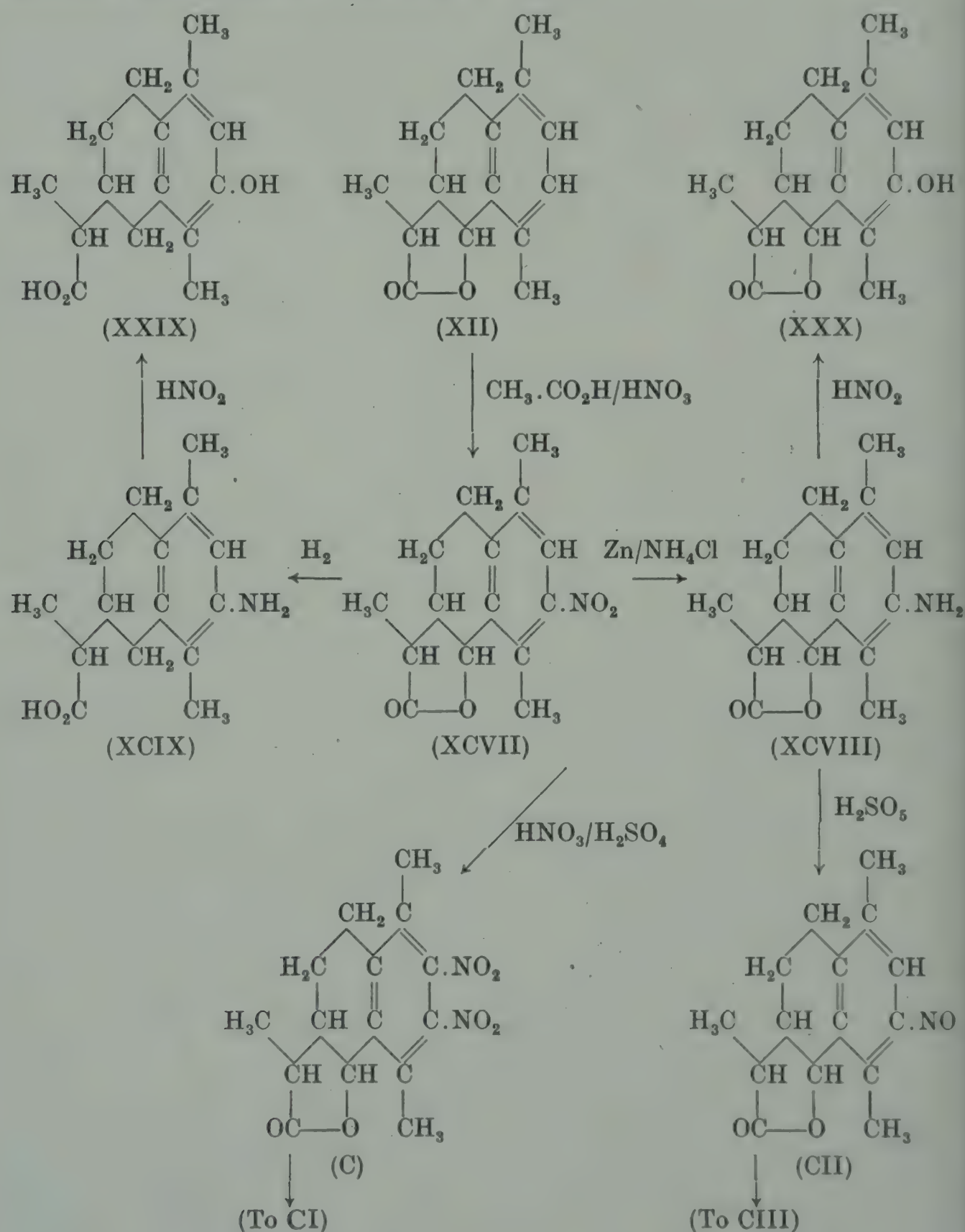
* Asahina and Momose (*Ber.* 1937, **70**, 812) give m.p. 265° decomp. for this substance.

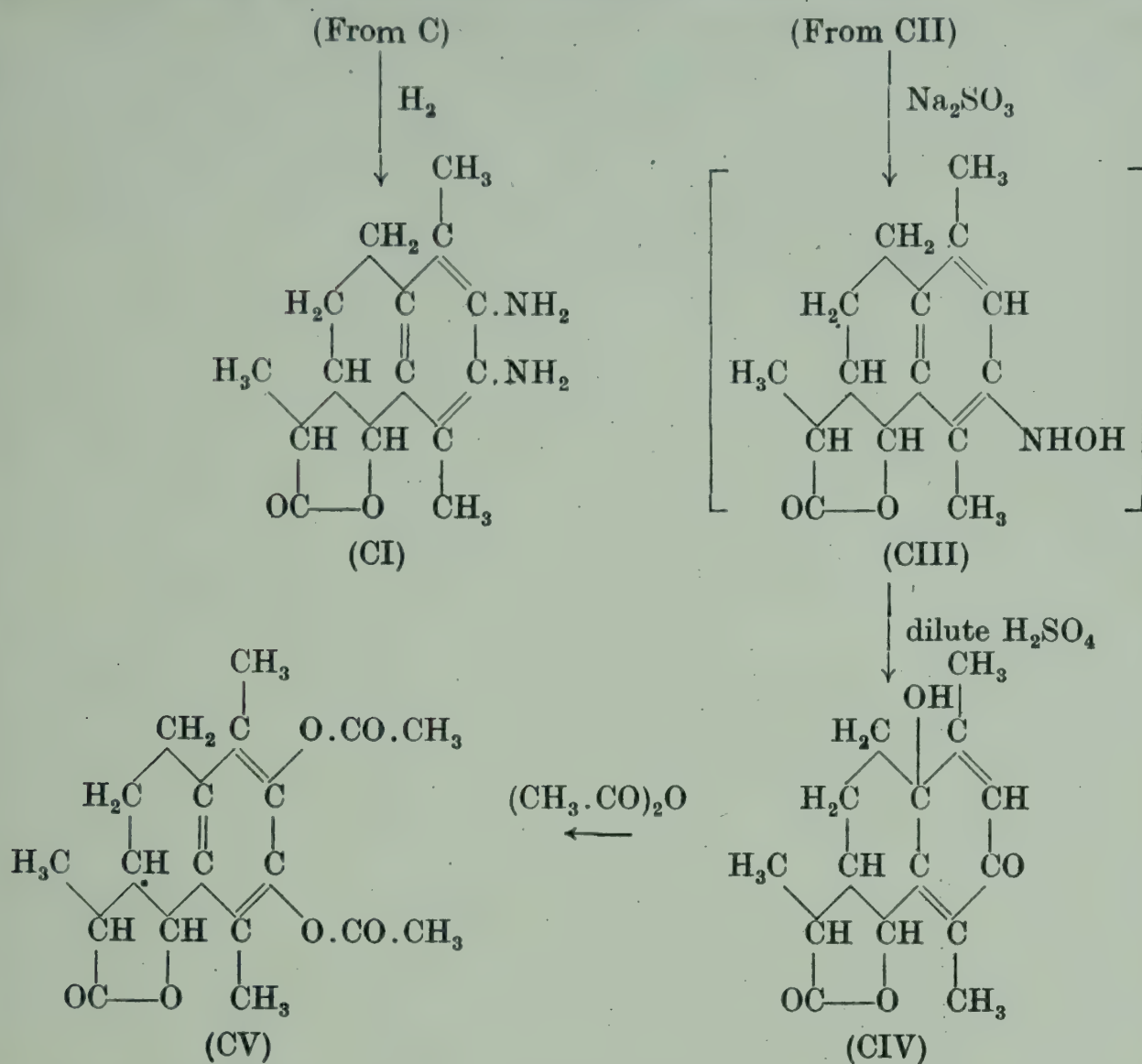
† Andreocci, *Gazz.* 1895, **25**, I, 507, 521, 528, 538; *Atti R. Accad. Lincei*, 1895 [v], **4**, I, 164.

‡ *Ber.* 1938, **71**, 1421; *Proc. Imp. Acad. (Tokyo)*, 1938, **14**, 112.

§ For the justification of the prefix *iso*- in this and the following compounds see Huang-Minlon, *J. Amer. C.S.* 1948, **70**, 611; compare Barton, *J. Org. Chem.* 1950, **15**, 466.

of the reaction product with dilute sulphuric acid was transformed to a *substance*, $C_{15}H_{18}O_4$, m.p. $222-223^\circ$, $[\alpha]_D^{24} - 324.8^\circ$, *oxime*, m.p. 188° , *acetate*, m.p. 204° , formulated as (CIV). On vigorous acetylation this compound gave a *diacetate*, possibly (CV), m.p. $200-201^\circ$. Asahina and Momose suggest that (CIV) may be the substance to which santonin is metabolised in the body of the dog, as its colour reactions are identical with those of the extracted bile of dogs after they have been injected with sodium santoninate (compare p. 250).



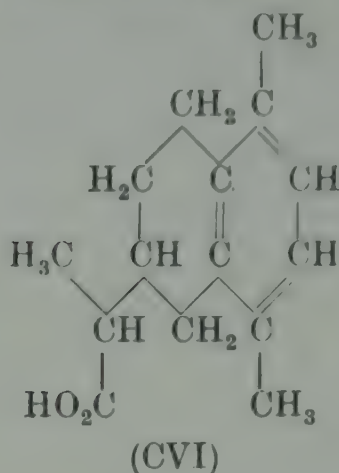


Grassi-Cristaldi* has suggested, from a study of the rates of reconversion of hyposantoninic and *isohyposantoninic* acids (see p. 268) to their corresponding lactones, hyposantonin and *isohyposantonin*, that the former acid has the *trans*-relationship of the hydroxyl group with respect to the propionic acid residue and that the latter acid has the *cis*-configuration. This assignment of configuration is also in agreement with the fact that both hyposantonin and *isohyposantonin* are reduced by zinc dust in acetic acid to *hyposantonous acid*, $C_{15}H_{20}O_2$ (CVI), m.p. 95.5° , $[\alpha]_D^{28} + 76.0^\circ$ (in alcohol), *methyl ester*, m.p. 43° , $[\alpha]_D^{28} + 79.1^\circ$ (in alcohol), which, from its rotatory power is obviously strictly comparable with *d*-santonous acid (see p. 265).[†] From the discussion on stereochemistry given on p. 268 it will be clear that hyposantonin should be represented as $C_5(d):C_6(d):C_{11}(d)$ and *isohyposantonin* as $C_5(l):C_6(d):C_{11}(d)$.[‡]

* Gazz. 1893, 23, I, 67.

† Grassi-Cristaldi, Gazz. 1896, 26, II, 459.

‡ Barton, *loc. cit.*



SANTONIN DERIVATIVES OF DOUBTFUL OR UNKNOWN CONSTITUTION

The action of light on santonin has been the subject of considerable study. When crystalline santonin is exposed to sunlight it turns yellow due, it is stated, to the formation of a stereoisomer *chromosantonin*, $C_{15}H_{18}O_3$, m.p. *ca.* 160° .^{*} Chromosantonin undergoes many of the same reactions as santonin and, moreover, in most cases is said to yield the same substances. It is stated further that the derivatives of chromosantonin on repeated crystallisation revert to those of santonin itself. On the basis of this and other evidence[†] it seems very probable that chromosantonin is merely an impure form of santonin.

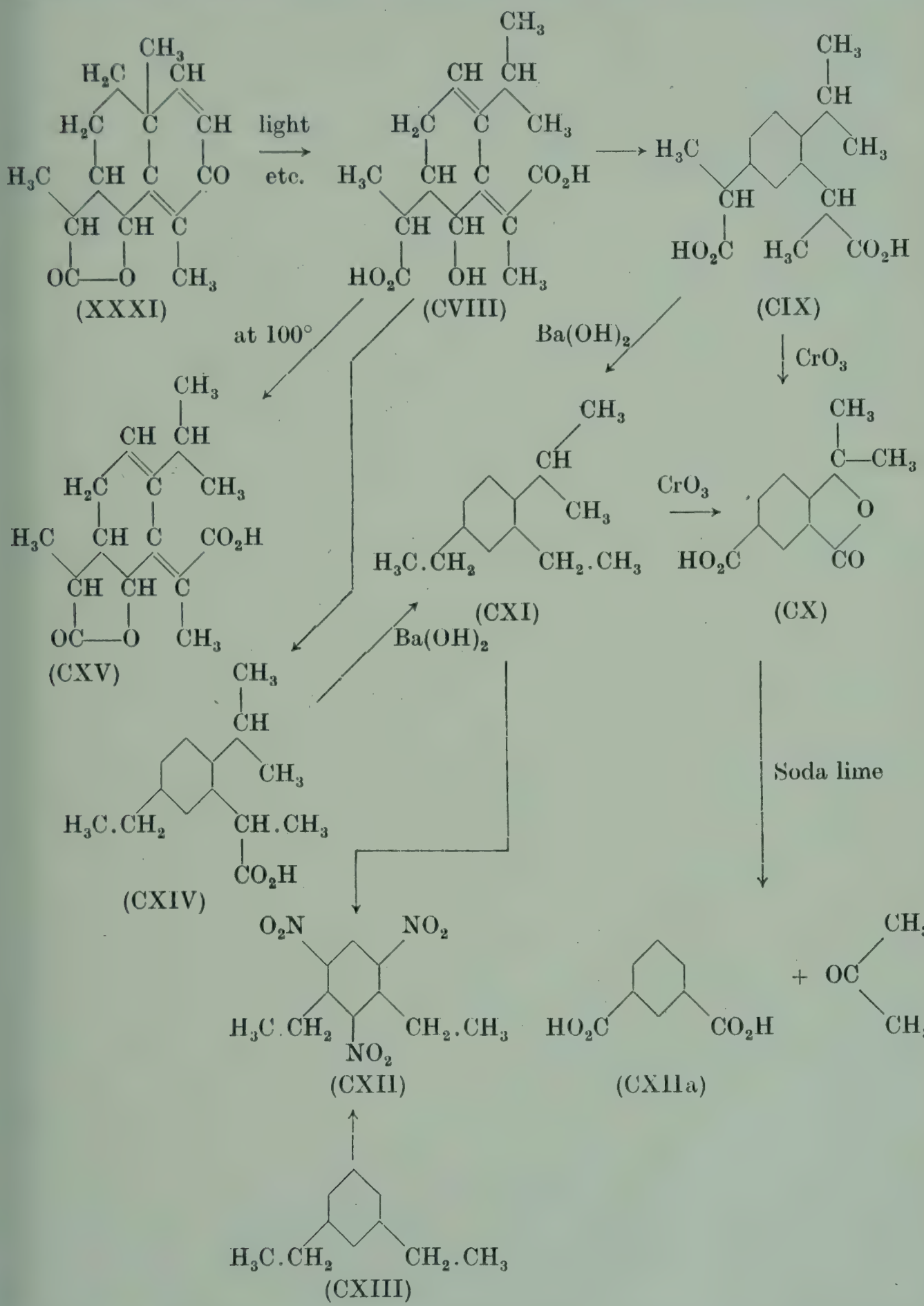
By the irradiation with sunlight of a solution of santonin in one equivalent of potassium hydroxide a dibasic acid, *photosantoninic acid*, $C_{15}H_{22}O_5$, possibly (CVIII), $[\alpha]_D^{20} -125.2^\circ$ (in alcohol), -119.3° (in chloroform) is formed.^{*} On treatment with alcoholic hydrochloric acid photosantoninic acid was dehydrated to a mixture of two stereoisomeric *dehydrophotosantoninic acids*, $C_{15}H_{20}O_4$, probably (CIX), (A), m.p. $138.5-139^\circ$, $[\alpha]_D +48^\circ$ (in alcohol) and (B) m.p. $134.5-135.5^\circ$, both of which, on heating above the melting-point, were converted into a third isomer (C) m.p. $133.5-134.5^\circ$. All these dehydrophotosantoninic acids gave the *dimethylphthalide* (CX), m.p. 205° , *ethyl ester*, m.p. 105° ,

^{*} Kahler, *Arch. Pharm.* 1830, **34**, 318; Trommsdorff, *Annalen*, 1834, **11**, 203; Heldt, *ibid.* 1847, **63**, 20; Montemartini, *Gazz.* 1902, **32**, I, 325; compare Wienhaus, *Ber.* 1913, **46**, 2839; Trendelenburg, *Arch. Path.* 1916, **79**, 206.

[†] Compare Piutti, *Atti R. Accad. Lincei*, 1913 [v], **22**, II, 203; and see Banchi and Infante, *Gazz.* 1931, **61**, 839.

^{*} Francesconi and Maggi, *Gazz.* 1903, **33**, II, 65; compare Sestini, *Gazz.* 1876, **6**, 359.

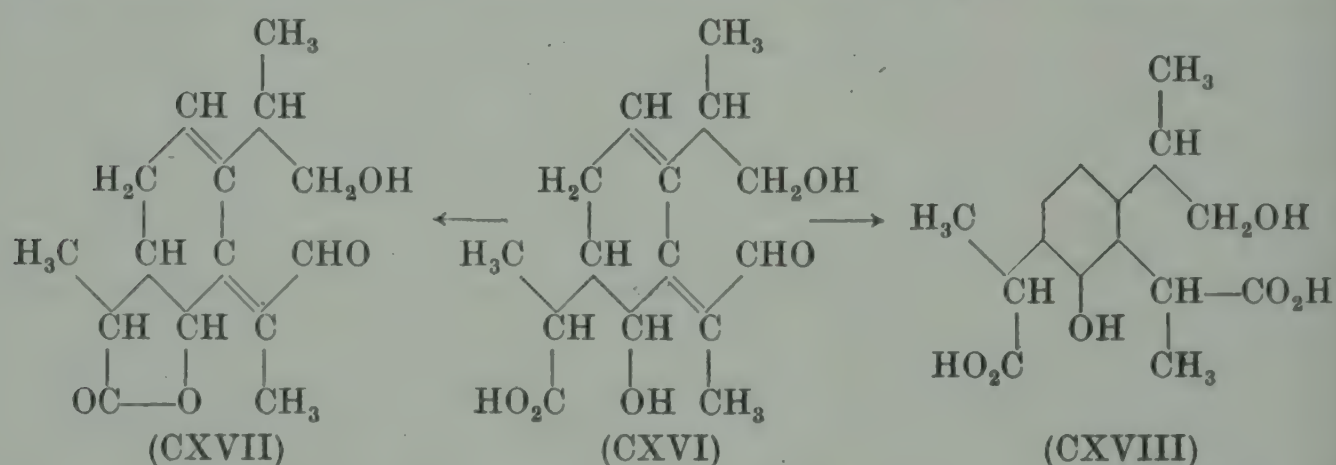
on oxidation with chromic acid, whilst by distillation with barium hydroxide they afforded 2:4-diethylisopropylbenzene (CXI), b.p.



224–226°, which likewise afforded (CX) on chromic acid oxidation. On distillation with soda lime (CX) afforded acetone and

isophthalic acid (CXIIa), whilst by nitration (CXI) was transformed to 2:4:6-trinitro-1:3-diethylbenzene (CXII), also prepared by the nitration of 1:3-diethylbenzene (CXIII). On heating with hydriodic acid or in an inert atmosphere photosantononic acid (CVIII) furnished *pyrophotosantononic acid*, $C_{14}H_{20}O_2$, m.p. 94.5° , formulated as (CXIV), which likewise gave (CXI) on heating with barium hydroxide, whilst by warming at 100° photosantononic acid gave the corresponding lactone, *photosantonlactonic acid*, $C_{15}H_{20}O_4$ (CXV), m.p. $154-155^\circ$, *ethyl ester*, m.p. 68° , $[\alpha]_D^{14} - 121.6^\circ$ (in alcohol).*

Santonin irradiated in alcoholic solution gives photosantonlactonic acid ethyl ester, also known as *photosantonin*, together with photosantononic acid (CVIII) and a substance, $C_{17}H_{24}O_4$, m.p. $154-155^\circ$, $[\alpha]_D^{13} + 76.8^\circ$ (in alcohol), of unknown constitution.[†] In acetic acid solution irradiation gives a compound, $C_{30}H_{38}O_7$, m.p. *ca.* 300° , of unknown constitution, photosantononic acid and an isomeric substance known as *isophotosantononic acid*,



$C_{15}H_{22}O_5$, possibly (CXVI), *oxime*, m.p. 151° , $[\alpha]_D^{19} + 170.3^\circ$ (in alcohol), *monoacetate*, m.p. 251° , $[\alpha]_D^{28} + 58.1^\circ$ (in chloroform), *diacetate*, m.p. $163-166^\circ$, which by warming at 100° or with acetyl chloride was transformed to *isophotosantonlactonic acid lactone*, $C_{15}H_{20}O_4$ (CXVII), m.p. $163-164^\circ$, $[\alpha]_D^{11} + 124.2^\circ$ (in alcohol), *oxime*, m.p. 220° decomp., *acetate*, m.p. 183° , $[\alpha]_D^{17} + 59^\circ$ (in alcohol), *acetate oxime*, m.p. 170° , *phenylhydrazone*, m.p. 239° decomp. On oxidation with acid potassium permanganate *isophotosantononic acid* gave the so-called *bishydroxyisophotosantononic acid*

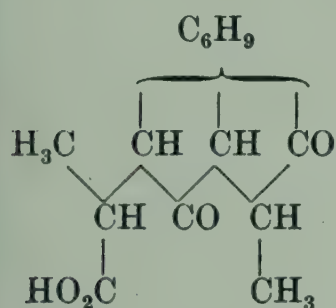
* Sestini and Danesi, *Gazz.* 1882, **12**, 83; Nasini, *ibid.* 1883, **13**, 378; Villavecchia, *Atti R. Accad. Lincei*, 1885 [iv], **1**, 722; *Ber.* 1885, **18**, 2859; Cannizzaro and Fabris, *Atti R. Accad. Lincei*, 1886 [iv], **2**, **1**, 448; *Ber.* 1886, **19**, 2260; Cannizzaro and Gucci, *Gazz.* 1893, **23**, **1**, 289; Francesconi and Venditti, *ibid.* 1902, **32**, **1**, 292, 310.

[†] Villavecchia, *Atti R. Accad. Lincei*, 1885 [iv], **1**, 723; *Ber.* 1885, **18**, 2861.

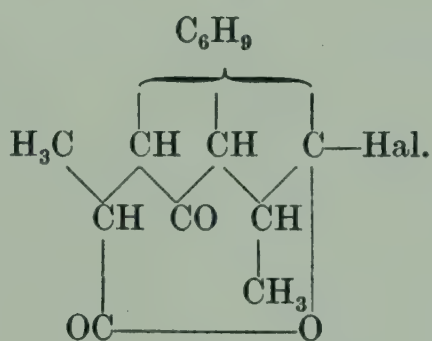
acid, $C_{15}H_{20}O_6$, m.p. $283-284^\circ$, $[\alpha]_D^{28} + 32.7^\circ$ (in chloroform), possibly represented by (CXVIII).^{*} In aqueous acetic acid solutions of santonin a variety of products including photosantoninic acid, isophotosantoninic acid, isophotosantoninic acid diacetate and the acetate of isophotosantoninic acid lactone have been recognised as being formed by irradiation with sunlight.[†] When santonin is dissolved in three equivalents of potassium hydroxide (compare above) and irradiated with sunlight it is said to form the so-called *photosantoninic acid*, $C_{30}H_{42}O_9$, m.p. $258-260^\circ$, $[\alpha]_D^{15} - 9.9^\circ$ (in alcohol), *diethyl ester*, m.p. 132° , of, as yet, unknown constitution. This dibasic acid with acetic anhydride gave a *dilactone monoacetate*, $C_{32}H_{40}O_8$, m.p. $199-200^\circ$, reconverted to photosantoninic acid on alkaline hydrolysis.[‡]

SANTONIC ACID

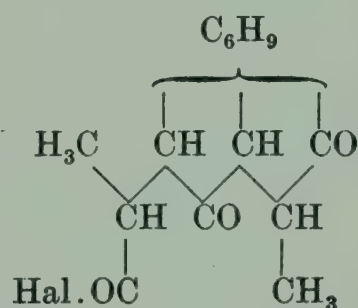
One of the most interesting aspects of the chemistry of santonin is the nature of the transformation of santoninic acid (see p. 250) to the isomeric *santoninic acid*, $C_{15}H_{20}O_4$, m.p. $170-172^\circ$, $[\alpha]_D^{20} - 74^\circ$



(CXIX)



(CXX)



(CXXI)

(in chloroform), $[\alpha]_D^9 - 74.1^\circ$ (in alcohol), *methyl ester*, m.p. 86° , $[\alpha]_D^{26.5} - 52.3^\circ$ (in chloroform), *ethyl ester*, m.p. $94-95^\circ$, $[\alpha]_D^{26.5} - 45.4^\circ$ (in chloroform).[§] This transformation, which is effected by the prolonged treatment of santonin with alkali, most conveniently, hot, saturated, barium hydroxide solution, was first

^{*} Villavecchia, *Atti R. Accad. Lincei*, 1885 [iv], 1, 722; *Ber.* 1885, 18, 2859; Cannizzaro and Fabris, *Atti R. Accad. Lincei*, 1886 [iv], 2, 1, 450; *Ber.* 1886, 19, 2261; Francesconi and Villavecchia, *Gazz.* 1902, 32, 1, 315; Francesconi and Venditti, *ibid.* 1902, 32, 1, 318.

[†] Cannizzaro and Fabris, *loc. cit.*; Francesconi and Venditti, *Gazz.* 1902, 32, 1, 297; compare Sestini, *ibid.* 1876, 6, 368; Villavecchia, *loc. cit.*

[‡] Francesconi and Maggi, *Gazz.* 1903, 33, 11, 66.

[§] The propyl, isobutyl, allyl and benzyl esters of santoninic acid have also been described; see references on page 296.

observed independently by Hooslef* and by Cannizzaro and Sestini.† Much of the earlier work on the chemistry of santonic acid and its functional derivatives will be found in the references quoted below.‡ For convenience santonic acid will, at this stage, be represented by the partial formula (CXIX).

Santonic acid has one reactive ketonic group, for it readily affords an *oxime*, m.p. 186–187°, $[\alpha]_D^{16^\circ} - 64.9^\circ$, *methyl ester*, m.p. 158–159°, $[\alpha]_D^{26^\circ} - 40.7^\circ$ (in alcohol), *ethyl ester*, m.p. 126–127°, $[\alpha]_D - 36.5^\circ$ (in alcohol), a *semicarbazone*, m.p. 183–185°, $[\alpha]_D^{25^\circ} + 13.4^\circ$ (in alcohol), a *phenylhydrazone*, m.p. 174°, *ethyl ester*, m.p. 115°, and an *azine*, m.p. 206–207°, $[\alpha]_D^{24.8^\circ} - 86.8^\circ$ (in acetic acid). With phosphorus trichloride, tribromide and triiodide santonic acid is transformed into the corresponding *chloride*, m.p. 170–171° decomp., $[\alpha]_D^{26.5^\circ} + 13.1^\circ$ (in chloroform), *bromide*, m.p. 145.5° decomp., $[\alpha]_D^{26^\circ} - 100.5^\circ$ (in chloroform) and *iodide*, m.p. 136° decomp., $[\alpha]_D^{26^\circ} - 99.2^\circ$ (in chloroform), respectively. These substances were formerly formulated as the equivalent of (CXX), but it would seem that this is unnecessary and that they are better regarded as normal acid halides (CXXI).§ On boiling with acetic anhydride santonic acid gives an acetyl derivative, m.p. 197–198°,|| which was formerly regarded as (CXXII), but which Wedekind and Engel¶ have now shown to be better represented as the mixed anhydride (CXXIII). With excess of hydroxylamine santonic acid gives a *dioxime*, m.p. 120–125° decomp., $[\alpha]_D - 102.4^\circ$ (in alcohol) and with excess of phenylhydrazine a *bisphenylhydrazone*, m.p. 95° decomp. This behaviour was not, however, regarded as conclusive evidence of the presence of two ketonic groups because the dioxime is not

* *Förhandlingar vid Skandnaviska Naturforskaremötet*, 1863, p. 304; see *Ber.* 1873, 6, 1471.

† *Gazz.* 1873, 3, 241; *Ber.* 1873, 6, 1201.

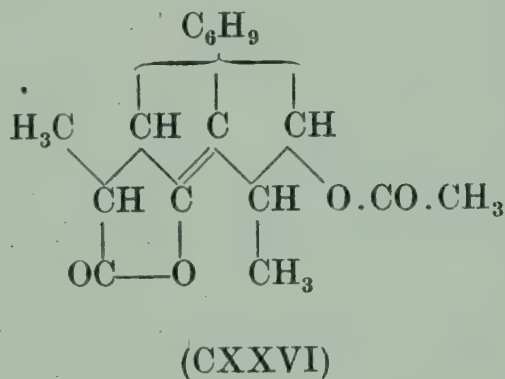
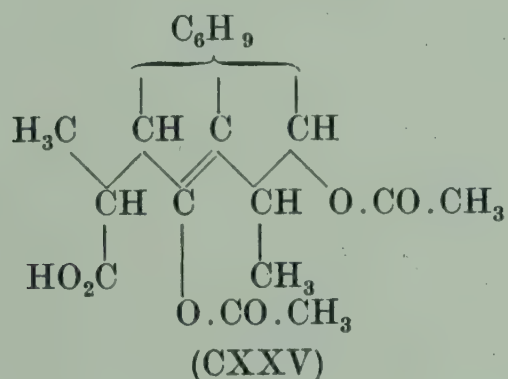
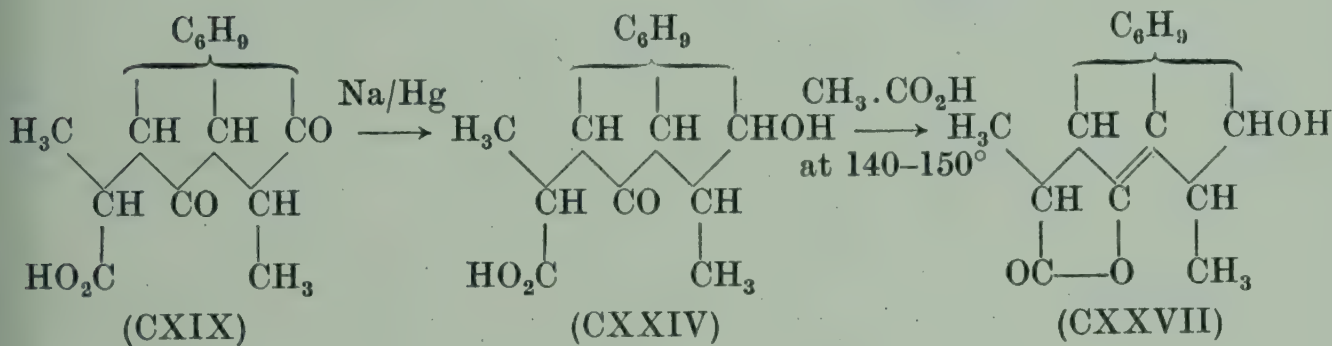
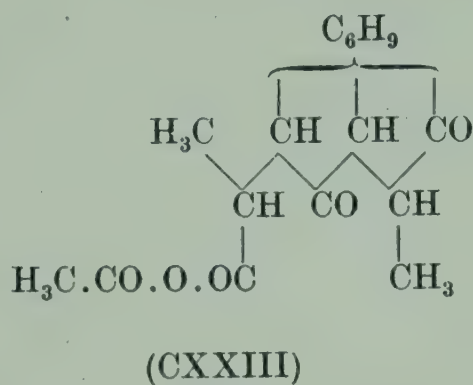
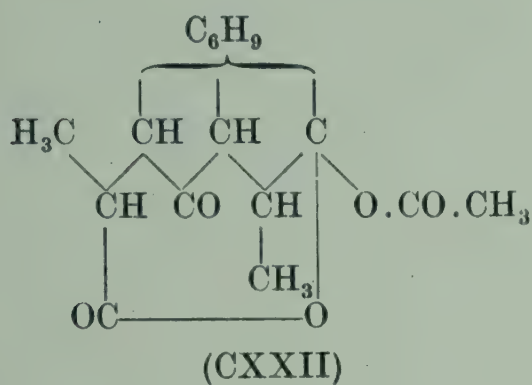
‡ Sestini, *Gazz.* 1876, 6, 148; Cannizzaro, *ibid.* 1876, 6, 355; Valente, *Atti R. Accad. Lincei Transunti*, 1877 [iii], 1, 26; Cannizzaro and Valente, *ibid.* 1877 [iii], 1, 27; Cannizzaro and Carnelutti, *ibid.* 1877 [iii], 1, 28; Cannizzaro and Valente, *Gazz.* 1878, 8, 309; Panebianco, *ibid.* 1878, 8, 351; *Ber.* 1880, 13, 2032; Cannizzaro and Carnelutti, *Gazz.* 1880, 10, 459; Carnelutti and Nasini, *ibid.* 1880, 10, 531, 538; *Ber.* 1880, 13, 2210; *Gazz.* 1883, 13, 165; Francesconi, *Gazz.* 1892, 22, 1, 186; Andreocci, *ibid.* 1895, 25, 1, 468; Wedekind, *Ber.* 1898, 31, 1680; 1899, 32, 1411; Francesconi, *Gazz.* 1899, 29, 11, 192, 224; Francesconi and Maggi, *ibid.* 1903, 33, 11, 71; Francesconi and Ferulli, *ibid.* 1903, 33, 1, 191, 199; Harries and Stahler, *Ber.* 1904, 37, 258; Francesconi and Cusmano, *Gazz.* 1908, 38, 11, 105; compare Francesconi, *Gazz.* 1895, 25, 11, 471.

§ See Wedekind and Engel, *J. pr. Chem.* 1934 [ii], 139, 115.

|| Compare, however, Schwenk and Goebel, *Ger. Pat.* 578,941.

¶ *Loc. cit.*

hydrolysed back to santonic acid with mineral acid.* Much better evidence as to the presence of a second sterically hindered carbonyl group in santonic acid in the γ -position with respect to the carboxyl grouping was provided by the following experiments.† By reduction with sodium amalgam santonic acid is converted into *dihydrosantonic acid*, $C_{15}H_{22}O_4$ (CXXIV), m.p. 190–192°,



methyl ester, m.p. 111°, *amide*, m.p. 190° decomp., which on vigorous acetylation gave a mixture of *dihydrosantonic acid diacetate* (CXXV), m.p. 232°, *methyl ester*, m.p. 151°, and the corresponding *acetyl lactone* (CXXVI), m.p. 204°. On heating at 140–150° in acetic acid solution dihydrosantonic acid afforded *dihydrosantonide*, $C_{15}H_{18}O_3$ (CXXVII), m.p. 155–156°, *acetate*, m.p. 204–204.5°, *benzoate*, m.p. 156.5–157°. Dihydrosantonic acid diacetate (CXXV), the acetyl lactone (CXXVI) and the lactone (CXXVII), were all reconverted to dihydrosantonic acid

* See Wedekind, *Arch. Pharm.* 1906, **244**, 635.

† Compare Wedekind and Engel, *loc. cit.*

on alkaline hydrolysis.* The presence of two ketonic groups in santonic acid was also supported by the observation of Wedekind† that two molecules of diazotised aniline couple with santonic acid to give *bisbenzeneazosantonic acid*, $C_{27}H_{28}O_4N_4$, m.p. 125–130°. An analogous *tetrazo-compound* is formed from santonic acid and diazotised *o*-tolidine.‡ Francesconi§ has attempted to establish the constitution of santonic acid by a study of its degradation products. On oxidation with alkaline potassium permanganate santonic acid gave a tetracarboxylic acid, α -santorinic acid, $C_{13}H_{18}O_8$, m.p. 176° decomp., $[\alpha]_D^{24} + 28.6^\circ$ (in water), *tetramethylester*, $[\alpha]_D^{28} + 56.0^\circ$ (in alcohol), which, on the basis of (CXIX) for santonic acid, may be formulated as (CXXIX). By heating with fuming hydrochloric acid at 180° α -santorinic acid was converted to its stereoisomer, β -santorinic acid, $C_{13}H_{18}O_8$, $[\alpha]_D + 29.2^\circ$ (in water), *tetramethyl ester*, m.p. 99–100°, $[\alpha]_D \pm 0^\circ$. β -Santorinic acid did not exhibit a melting-point, but on heating at 135–150° was transformed into its *monoanhydride*, $C_{13}H_{16}O_7$, m.p. 192–193°, also prepared by heating α -santorinic acid at *ca.* 180°. On treatment with cold acetic anhydride α -santorinic acid was dehydrated to its *dianhydride*, $C_{13}H_{14}O_6$, m.p. 134–135°, but using warm acetic anhydride the *dianhydride*, m.p. 151–152°, of β -santorinic acid was obtained, which was also prepared by the action of the same reagent on β -santorinic acid and its monoanhydride. By heating α -santorinic acid or the monoanhydride of β -santorinic acid at 260–280° the *anhydride*, m.p. *ca.* 150° to *ca.* 186°, of a cyclic ketonic dicarboxylic acid was produced.|| This ketonic dicarboxylic acid, known as *keto- β -santorinic acid*, $C_{12}H_{16}O_5$, m.p. 213–214° decomp., $[\alpha]_D - 128.1^\circ$ (in alcohol), *oxime*, m.p. 197–198°, *methyl ester*, *hemihydrate*, m.p. 90–91°, anhydrous, m.p. 135°, *dimethyl ester*, m.p. 91–92°, $[\alpha]_D$ *ca.* -108° (in alcohol), *oxime*, m.p. 120–121°, $[\alpha]_D + 25.6^\circ$ (in alcohol), *semicarbazone*, m.p. 168°, was readily obtained by

* Cannizzaro, *Gazz.* 1876, **6**, 341; Cannizzaro and Valente, *Atti R. Accad. Lincei. Memori*, 1877 [iii], **2**, 547; *Gazz.* 1878, **8**, 317; Harries and Stähler, *Ber.* 1904, **37**, 258; Wedekind and Engel, *J. pr. Chem.* 1934 [ii], **139**, 115.

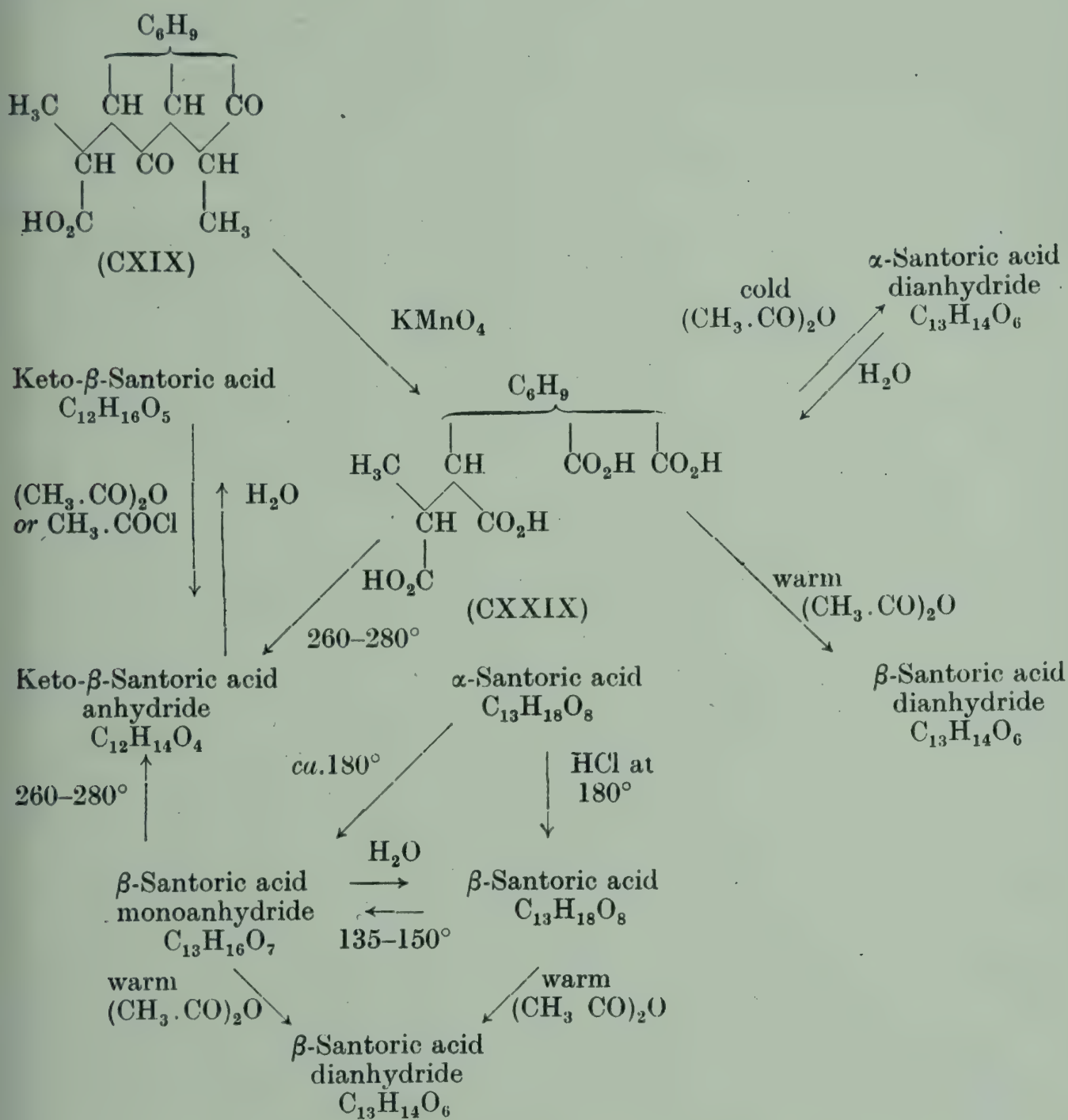
† *Ber.* 1898, **31**, 1681; Wedekind and Schmidt, *ibid.* 1903, **36**, 1387.

‡ Wedekind, *Ber.* 1903, **36**, 1395.

§ *Gazz.* 1892, **22**, **i**, 197; 1893, **23**, **ii**, 457; *Atti R. Accad. Lincei*, 1896 [v], **5**, **ii**, 218; *Gazz.* 1899, **29**, **ii**, 206, 215, 237.

|| Compare Wedekind and Jackh, *J. pr. Chem.* 1934 [ii], **139**, 129, who have prepared a cyclic *ketone anhydride*, m.p. 203–204°, *oxime*, decomp. 223°, by the action of acetic anhydride on α -santorinic acid.

hydration of the anhydride, and could be reconverted to the anhydride by the action of acetic anhydride or of acetyl chloride. The relationships between the α - and β -santoronic acids and the substances mentioned above can be conveniently summarised in the appended scheme.



On fusing α -santoronic acid with sodium hydroxide at 300° a mixture of two isomeric tricarboxylic acids, α -santoronic acid, $\text{C}_{10}\text{H}_{16}\text{O}_6$, m.p. $125-126^\circ$, optically inactive, and β -santoronic acid, not isolated in a state of purity, were obtained. But using the same reagent at $380-400^\circ$, a cyclic ketone, *santorone*, $\text{C}_8\text{H}_{14}\text{O}$, b.p. $169-171^\circ$, *oxime*, m.p. $117.5-118.5^\circ$, *semicarbazone*, m.p. $174-175^\circ$, was produced, which was reduced by digestion with

hydriodic acid and red phosphorus to a saturated hydrocarbon, *santorene*, C_8H_{16} , b.p. 133–134°. By heating at 200–210° with a solution of iodine in acetic acid α -santorinic acid gave a *tetracarboxylic acid*, $C_{13}H_{14}O_8$, m.p. 250–251°, $[\alpha]_D^{24} + 42.8^\circ$ (in alcohol).

All attempts to hydrogenate santonic acid* were unsuccessful and this observation, together with the fact that α -santorinic acid was stable to potassium permanganate, were taken to imply the absence of an ethylenic linkage in santonic acid. This view was in agreement with the experimental findings of Cannizzaro and Amato,[†] who observed that on reduction with hydriodic acid and red phosphorus santonic acid gave, although in small yield, a saturated tricyclic hydrocarbon, the so-called *santone*, $C_{15}H_{26}$, b.p. 235–245°, 110–112°/5 mm., and the corresponding *iodide*, $C_{15}H_{25}I$, b.p. 143–145°/5 mm. It was concluded therefore that santonic acid was tricyclic and that the derived α -santorinic acid (CXXIX) must be monocyclic.

Wedekind and Jackh[‡] endeavoured to obtain further insight into the constitution of santonic acid by oxidative degradation. By oxidation with alkaline hydrogen peroxide santonic acid afforded an unsaturated ketonic acid, *aposantonic acid*, $C_{14}H_{20}O_3$, m.p. 164–165°, $[\alpha]_D^{18} + 98.9^\circ$ (in methyl alcohol), *oxime*, decomp. 185–186°, which was easily hydrogenated catalytically to the saturated *dihydroaposantonic acid*, $C_{14}H_{22}O_3$, decomp. 205–206°, *oxime*, decomp. 188–189°, and which by oxidation with chromic acid furnished a saturated *diketo-lactone*, $C_{14}H_{18}O_4$, m.p. 159–160°, *dioxime*, decomp. 228°, hydrolysed by alkali to the corresponding *hydroxy-carboxylic acid*, $C_{14}H_{20}O_5$, decomp. 200–202°. On oxidation with potassium hypobromite santonic acid gave *hydroxysantonic acid*, $C_{15}H_{20}O_6$, *hemihydrate*, decomp. 215°, *anhydrous*, m.p. 198°, $[\alpha]_D^{18} + 15.6^\circ$ (in methyl alcohol), *methyl ester*, m.p. 87–90° decomp., *diacetate*, decomp. 192° (*methyl ester*, m.p. 142°).

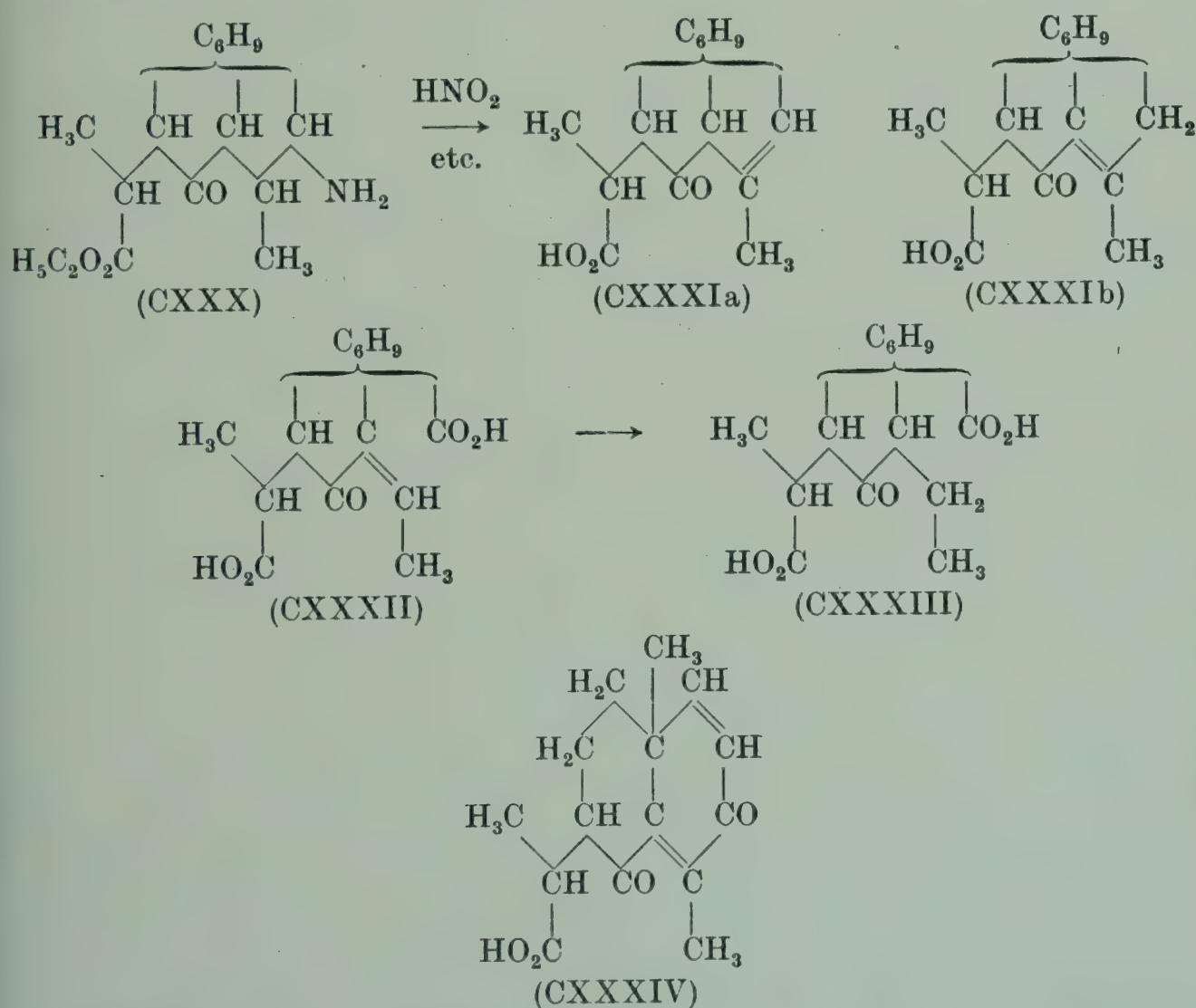
When ethyl santonate oxime is reduced with sodium amalgam

* Wienhaus and Oettingen, *Annalen*, 1913, **397**, 226; Wedekind and Engel, *J. pr. Chem.* 1934 [ii], **139**, 115.

[†] *Gazz.* 1874, **4**, 446; *Ber.* 1874, **7**, 1104; Cannizzaro and Carnelutti, *Gazz.* 1878, **8**, 318.

[‡] *J. pr. Chem.* 1934 [ii], **139**, 129; compare Medvedev, *Trans. Karpov. Inst. Chem.* 1924, No. 3, p. 41; Medvedev and Alekseeva, *Trans. Karpov. Inst. Chem.* 1926, No. 5, p. 57; Abkin and Medvedev, *J. Gen. Chem. U.S.S.R.* 1934, **4**, 1407.

it behaves similarly to santonin oxime (see p. 252) and gives *ethyl aminosantonate* (CXXX), m.p. 140–141°, $[\alpha]_D^{18} + 131.3^\circ$ (in alcohol), which by treatment with nitrous acid affords *hyposantononic acid*, $C_{15}H_{18}O_3$, m.p. 135–136°, which was represented by (CXXXI).^{*} With nitrous acid santonic acid oxime reacts to give the so-called *santol-hydroxamic acid anhydride*, $C_{15}H_{21}O_4N$, m.p. 235° decomp., $[\alpha]_D^{25} - 214.3^\circ$ (in alcohol), which with concentrated sulphuric acid gives *santolic acid*, $C_{15}H_{20}O_5$, m.p. 178–180° decomp., $[\alpha]_D^{27} + 90.7^\circ$ (in alcohol).[†] Wedekind and Jackh[‡] found that santolic acid could be easily prepared by the action of sulphuric acid on santonic acid oxime and suggested that its formation must be comparable to the conversion of camphor-oxime to α -campholenic acid by the same reagent (see Vol. II, p. 437). In agreement with this view santolic acid, which was represented by (CXXXII), was easily reduced by catalytic hydrogenation to the saturated *dihydrosantolic acid*, $C_{15}H_{22}O_5$ (CXXXIII), m.p. 160° decomp.



^{*} Francesconi, *Gazz.* 1892, **22**, 1, 192.

[†] Francesconi and Ferulli, *Gazz.* 1903, **33**, 1, 188.

[‡] *Loc. cit*

When treated with bromine in chloroform solution in the presence of water, santonic acid is oxidised to the yellow *triketo-santonic acid*, $C_{15}H_{14}O_7$, m.p. 234° decomp., $[\alpha]_D^{14} - 458.7^\circ$ (in alcohol), *ethyl ester*, m.p. $157-158^\circ$, $[\alpha]_D - 394.1^\circ$ (in alcohol), the constitution of which is unknown.*

Wedekind and Engel† attempted to establish how far the structure of the santonin molecule may be modified without affecting its property of rearrangement with alkali. α -Tetrahydrosantonin (see p. 256), santonin α -oxide (see p. 260), *d*-desmotroposantonin (see p. 257), monochlorosantonin (see p. 275) and, most interesting of all, artemionic acid (CXXXIV) (see p. 316) were all unaffected by alkali under conditions which led to the smooth formation of santonic acid from santonin. Wedekind and Engel concluded from these and other experiments that the carbonyl group of santonic acid did not correspond to that originally present in santoninic acid. This conclusion was, however, disproved by the work of Asahina and Momose‡ on α -hydroxysantonin, to which reference has already been briefly made on p. 281. When α -hydroxysantonin (LXXVIIIa) or (LXXVIIIb) is boiled with sodium hydroxide solution a neutral *diketone*, $C_{12}H_{16}O_2$, m.p. $106-107^\circ$, $[\alpha]_D^{22} - 108.9^\circ$ (in alcohol), *dioxime*, m.p. $244-245^\circ$ decomp., *semicarbazone*, m.p. 240° decomp., *enol acetate*, b.p. $134-135^\circ/3$ mm., is formed. The reaction may be regarded as involving firstly the dehydration of α -hydroxysantonin to the $\alpha:\beta$ -unsaturated acid (CXXXV), followed by the rearrangement of this to (CXXXVI) and finally hydrolysis to the diketone, represented by (CXXXVII), and pyruvic acid.§ In agreement with this view the diketone (CXXXVII) was oxidised by alkaline potassium permanganate with loss of two carbon atoms, to a *tricarboxylic acid*, $C_{10}H_{14}O_6$, m.p. $164-165^\circ$, $[\alpha]_D^{22} - 40.0^\circ$ (in water), which may be represented by (CXXXVIII).

When santonic acid is treated with warm concentrated sulphuric acid it is dehydrated to an unsaturated ketonic lactone, *metasantonin*, $C_{15}H_{18}O_3$, m.p. 137° , $[\alpha]_D^{26} - 223.5^\circ$ (in chloroform), *oxime*, m.p. 220° , $[\alpha]_D^{25} - 377^\circ$ (in alcohol), readily

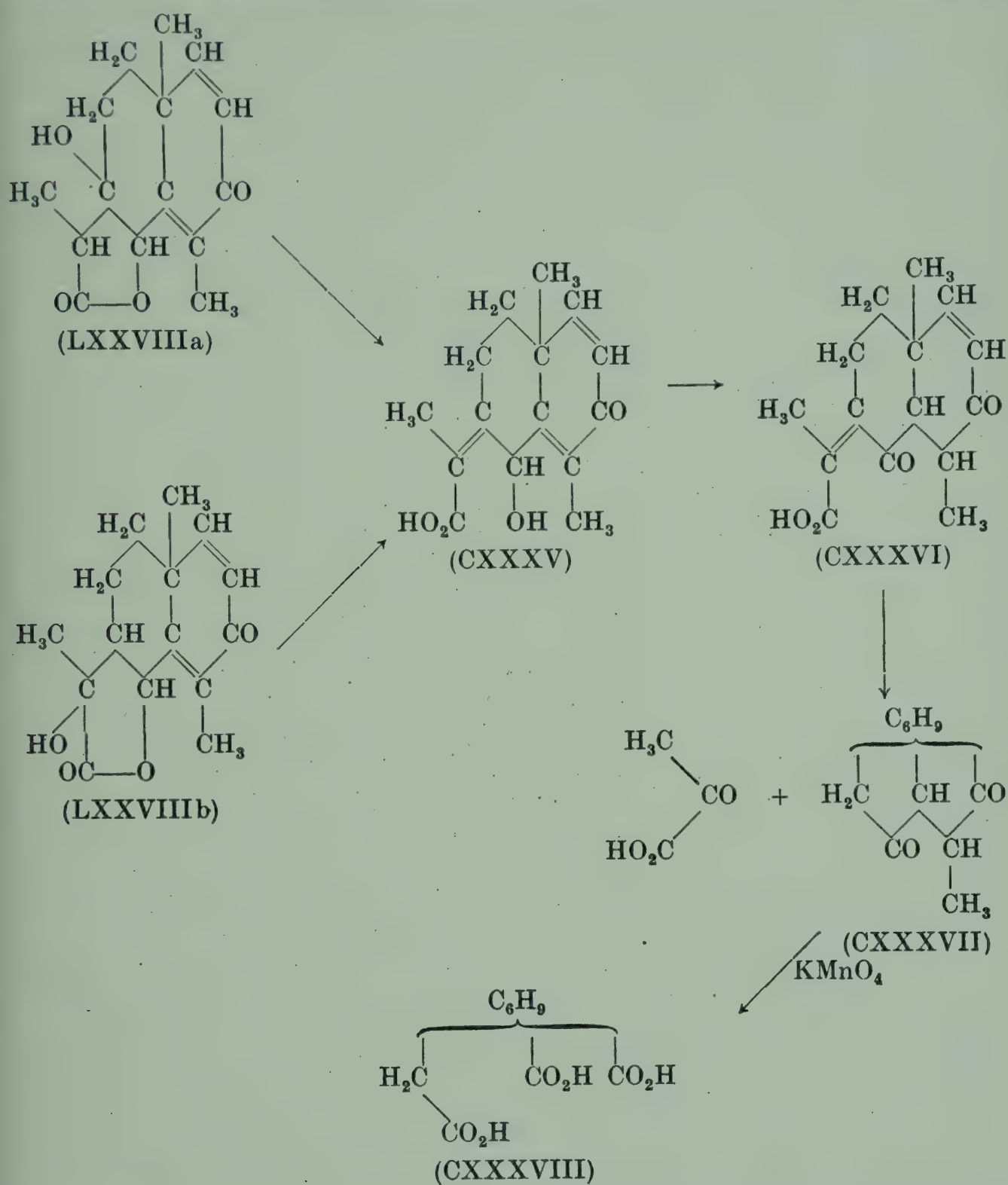
* Francesconi, *Gazz.* 1899, **29**, II, 219, 252.

† *J. pr. Chem.* 1934 [ii], **139**, 115.

‡ *Ber.* 1937, **70**, 812.

§ Compare the hydrolysis of pulegone to 3-methylcyclohexanone and acetone, Vol. I, p. 371.

reduced by zinc dust in hydrochloric acid or by catalytic hydrogenation to the saturated lactone, *dihydrometasantonin*, $C_{15}H_{20}O_3$,



m.p. 181–182°, $[\alpha]_D^{25} - 102.6^\circ$ (in chloroform), *oxime*, m.p. 196°, $[\alpha]_D^{25} - 239^\circ$ (in alcohol).*

On alkaline hydrolysis metasantonin furnishes a stereoisomer of santonic acid, *metasantonic acid*, $C_{15}H_{20}O_4$, m.p. 164–167°

* Cannizzaro and Valente, *Atti R. Accad. Lincei, Transunti*, 1879 [iii], 3, 242; Cernelutti and Nasini, *Gazz.* 1880, 10, 528, 538; *Ber.* 1880, 13, 2210; Francesconi, *Gazz.* 1895, 25, II, 465; Wienhaus and Oettingen, *Annalen*, 1913, 397, 219; compare Francesconi, *Gazz.* 1899, 29, II, 235.

decomp., $[\alpha]_D - 94^\circ$ (in chloroform), *dioxime*, m.p. $115-120^\circ$, *methyl ester*, m.p. $101.5-102.5^\circ$ (*oxime*, m.p. 171° , $[\alpha]_D - 175^\circ$ (in alcohol)), *ethyl ester*, m.p. ca. 50° (*oxime*, m.p. 166°), which can also be prepared by the action of heat or acetic acid at $280-290^\circ$ on santonic acid or by oxidation of dihydrosantonic acid (see p. 297) with silver oxide. With phosphorus trichloride or acetyl chloride metasantonic acid gives a *chloride*, m.p. 139° , whilst with acetic anhydride it gives what is presumably a *mixed anhydride*, m.p. $202-203^\circ$. More energetic acetylation leads to the formation of a *diacetyl derivative*, m.p. 207° , which can also be prepared from santonic acid. On oxidation with potassium permanganate metasantonic acid affords α -santonic acid (CXXIX) (see p. 298) in the same way as does santonic acid.*

When santonic acid is refluxed for many hours with acetic acid and the residue then heated to 180° , an isomer of metasantonin, *santonide*, $C_{15}H_{18}O_3$, m.p. 127.5° , $[\alpha]_D^{20^\circ} + 693^\circ$ (in alcohol), $[\alpha]_D^{20^\circ}$ ca. $+750^\circ$ (in chloroform), results, which can also be obtained by heating santonic acid with acetic acid at 200° . Santonide on hydrolysis gives the so-called *isosantonic acid*, $C_{15}H_{20}O_4$, m.p. 152° , $[\alpha]_D^{25^\circ} - 73.9^\circ$ (in chloroform), *methyl ester*, m.p. $69-70^\circ$, $[\alpha]_D^{27^\circ} - 50.2^\circ$ (in chloroform), *ethyl ester*, m.p. 76° .†

However, if in the preparation of santonide from santonic acid the final temperature is raised to $260-300^\circ$, a further isomer of metasantonin, *parasantonide*, m.p. 110° , $[\alpha]_D^{26^\circ} + 897.3^\circ$ (in chloroform), is formed. This lactone can also be prepared by heating metasantonic acid at $260-300^\circ$ and gives on hydrolysis the corresponding acid, *parasantonic acid*, $C_{15}H_{20}O_4$, m.p. 170° , $[\alpha]_D^{26^\circ} - 98.5^\circ$ (in chloroform), *methyl ester*, m.p. $183-184^\circ$, $[\alpha]_D^{26.5^\circ} - 108.9^\circ$ (in chloroform), *ethyl ester*, m.p. 173° , $[\alpha]_D^{26^\circ} - 100.0^\circ$ (in chloroform). With alcoholic ammonia parasantonide afforded *parasantonide imide*, m.p. $216-217^\circ$, $[\alpha]_D + 1135^\circ$ (in alcohol), *acetyl derivative*, m.p. $169-170^\circ$, $[\alpha]_D^{25^\circ} + 697.2^\circ$ (in alcohol), in agreement with its formulation as a lactone.‡ By

* Cannizzaro, *Gazz.* 1876, **6**, 345; Cannizzaro and Valente, *Atti R. Accad. Lincei, Memorie*, 1878 [iii], **2**, 548; *Gazz.* 1878, **8**, 310; *Atti R. Accad. Lincei*, 1879 [iii], **3**, 243; Francesconi, *Gazz.* 1895, **25**, II, 469; 1899, **29**, II, 187, 202, 233.

† Cannizzaro and Valente, *Gazz.* 1878, **8**, 315; Cannizzaro and Nasini, *ibid.* 1880, **10**, 529; Nasini, *ibid.* 1883, **13**, 149; Francesconi, *ibid.* 1895, **25**, II, 471.

‡ Cannizzaro and Valente, *Gazz.* 1875, **8**, 315; Carnelutti and Nasini, *ibid.* 1880, **10**, 530, 538; *Ber.* 1880, **13**, 2210; Nasini, *Gazz.* 1883, **13**, 154; Francesconi, *Atti R. Accad. Lincei*, 1903 [v], **12**, II, 205; compare Francesconi, *Gazz.* 1895, **25**, II, 474.

treatment with acetic anhydride parasantononic acid was reconverted to parasantonide. When treated with bromine in chloroform solution parasantononic acid was converted into *dibromoparasantononic acid*, $C_{15}H_{18}O_4Br_2$, m.p. 176–177° decomp., $[\alpha]_D + 28^\circ$ (in alcohol), which was reduced by zinc dust in acetic acid solution to parasantononic acid and which with alkali carbonate solution was converted into *dihydroxyparasantononic acid*, $C_{15}H_{20}O_6$, m.p. 206–207°, $[\alpha]_D^{25.4^\circ} - 109.7^\circ$ (in alcohol). With sodium hydroxide solution dibromoparasantononic acid gave *dehydrodihydroxyparasantononic acid*, $C_{15}H_{18}O_5$, m.p. 187–188°, $[\alpha]_D^{27.2^\circ} - 31.6^\circ$ (in alcohol).* Santonide and parasantonide are chiefly remarkable for their very high optical rotatory powers and have been examined from this point of view by Mitchell and Schwarzwald.†

The production of the saturated hydrocarbon santone by the action of hydriodic acid and red phosphorus on santonic acid has been briefly referred to on p. 300. The main product of this reaction is, however, a mixture of two probably stereoisomeric unsaturated lactones, α -metasantonin, m.p. 160.5°, b.p. 238–240°/10 mm., $[\alpha]_D^{26^\circ} + 118.8^\circ$ (in chloroform) and β -metasantonin, m.p. 136°, $[\alpha]_D^{20^\circ} + 124^\circ$ (in chloroform). α -Metasantonin was also prepared by the similar reductive treatment of parasantononic acid and by the action of concentrated sulphuric acid on parasantononic acid or on parasantonide. With bromine α -metasantonin gave *monobromo- α -metasantonin*, m.p. 212°, or *dibromo- α -metasantonin*, m.p. 184°, depending upon the conditions used. β -Metasantonin reacted similarly with bromine to give a *monobromo-derivative*, m.p. 114°, or a *dibromo-derivative*, m.p. 186° decomp.‡

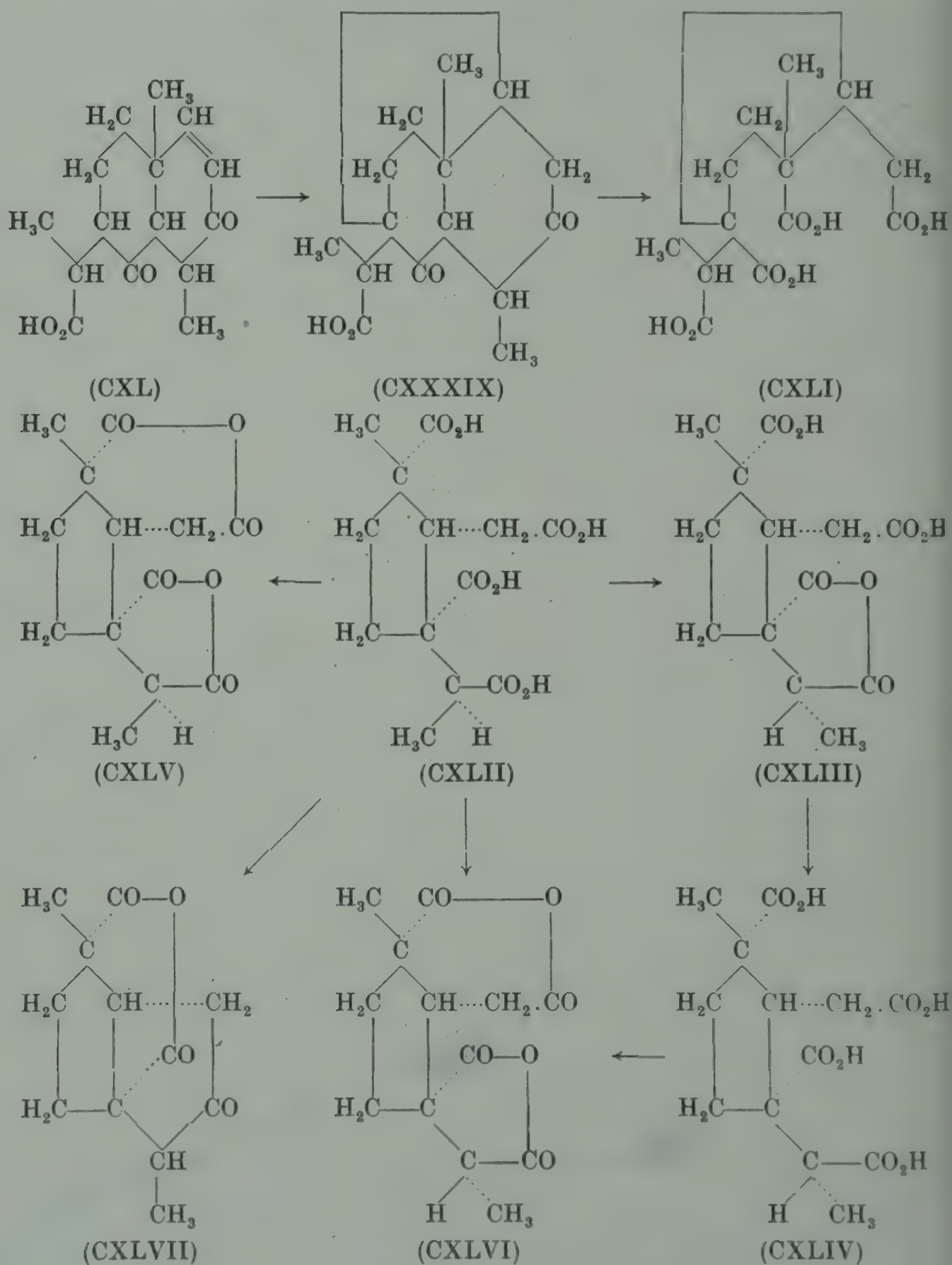
For many years the formulation of santonic acid remained one of the outstanding problems in santonin chemistry. The interpretation of the experimental results obtained up to 1948 has been briefly summarised in the above paragraphs. Recently in a brilliant analysis of the problem, Woodward, Brutschy and Baer§ advanced the formula (CXXXIX), the third and hitherto

* Francesconi, *Atti R. Accad. Lincei*, 1903 [v], 12, II, 268; other derivatives of parasantononic acid will be found described in this reference. † *J.C.S.* 1939, p. 889.

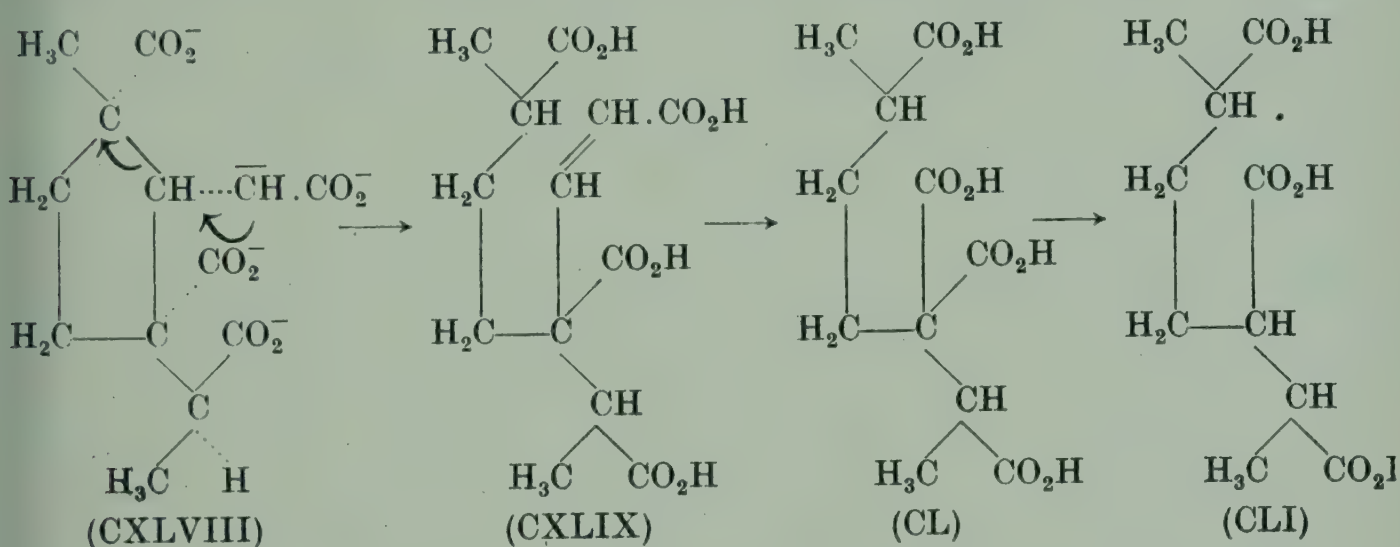
‡ Cannizzaro and Carnelutti, *Gazz.* 1878, 8, 320; 1880, 10, 462; Carnelutti and Nasini, *ibid.* 1880, 10, 527, 538; *Ber.* 1880, 13, 2210; Nasini, *Gazz.* 1883, 13, 156.

§ *J. Amer. C.S.* 1948, 70, 4216.

uncharacterised ring being regarded as formed by an internal Michael condensation from the precursor (CXL). This formula is undoubtedly correct and, as the American workers have shown, it explains in a very convincing manner the more important degradation reactions of santonic acid. α -Santoric acid (p. 298) must be represented by (CXLI) which can more conveniently be



written as (CXLII). β -Santoronic acid monoanhydride (p. 298), formed by the action of heat on α -santoronic acid, must very probably be (CXLIII), on which basis β -santoronic acid can be regarded as (CXLIV). Similarly α -santoronic acid dianhydride must be represented as (CXLV) and the analogous β -santoronic acid derivative by (CXLVI). Keto- β -santoronic acid anhydride, formed (p. 298) by the action of high temperatures on α -santoronic acid or on β -santoronic acid monoanhydride, may be represented as (CXLVII). The degradation (p. 299) of α -santoronic acid by fusion with potassium hydroxide must be represented in the manner indicated as an inverse Michael reaction proceeding as in (CXLVIII),* followed by "hydrolysis" of the $\alpha:\beta$ -unsaturated acid (CXLIX), oxidation of the aldehyde thus formed to the



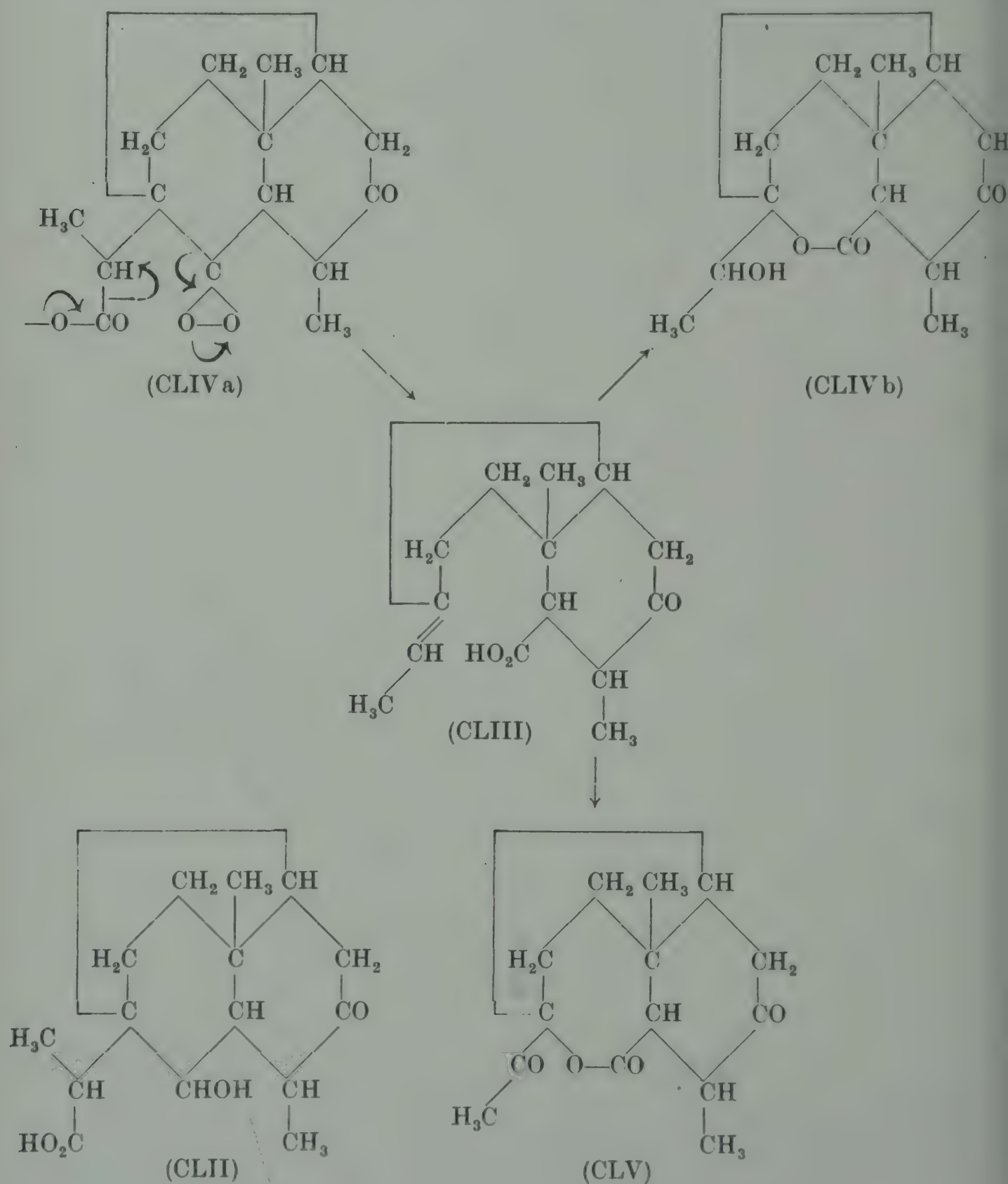
corresponding malonic acid (CL) and decarboxylation to α -santoronic acid (CLI). The correctness of the α -santoronic acid formula was proved by synthesis. The cyclic ketone santorone, formed (p. 299) from α -santoronic acid by fusion with alkali, must be 1:3-dimethylcyclohexanone and the hydrocarbon, santorene, formed therefrom, must be 1:3-dimethylcyclohexane.

According to Woodward, Brutschy and Baer,[†] space models of the santonic acid formula (CXXXIX) (p. 306) indicate that it is the keto-group in the γ -position to the carboxyl which is the *less* sterically hindered. Thus dihydrosantoronic acid must be regarded as (CLII), and not in the manner suggested (p. 297) by the earlier workers. An analogous revision is required in our views (p. 297)

* The alternative direction for the inverse Michael reaction leads to the same formula (CLI) for α -santoronic acid.

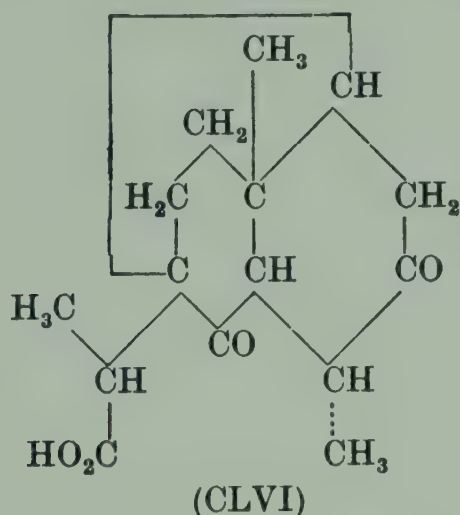
[†] *Loc. cit.*

with regard to dihydrosantonide, dihydrosantononic acid diacetate and the corresponding acetyl lactone. Similarly it is considered that it is the γ -keto group which is attacked by alkaline hydrogen peroxide in the formation of aposantononic acid (p. 300) which is formulated as (CLIII). The reaction is regarded as proceeding through the peroxide (CLIV a) in the manner indicated. In agreement with this view treatment of aposantononic acid with perbenzoic acid gave not an oxide but an acetylateable *hydroxy-*

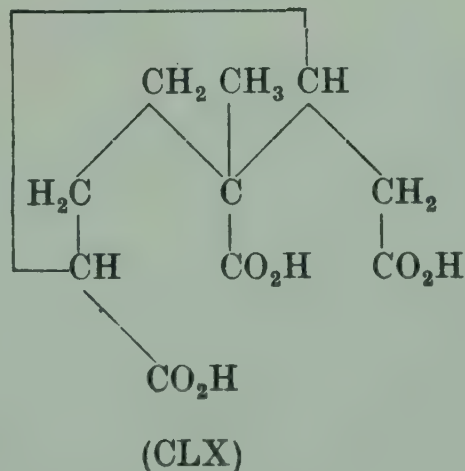
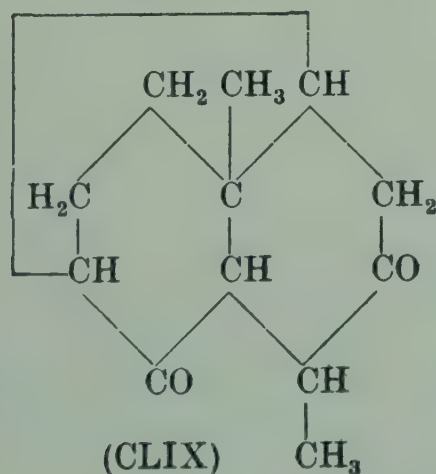
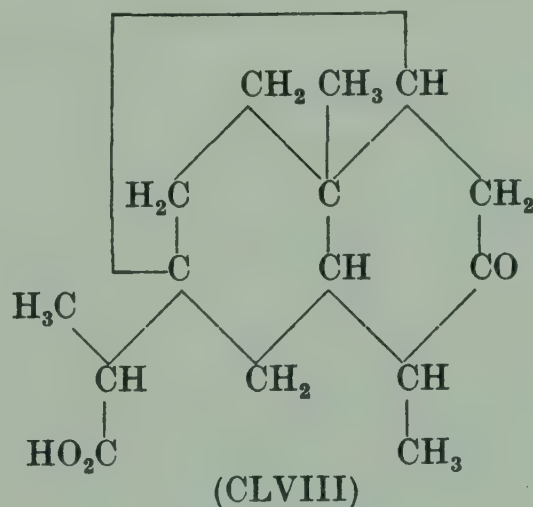
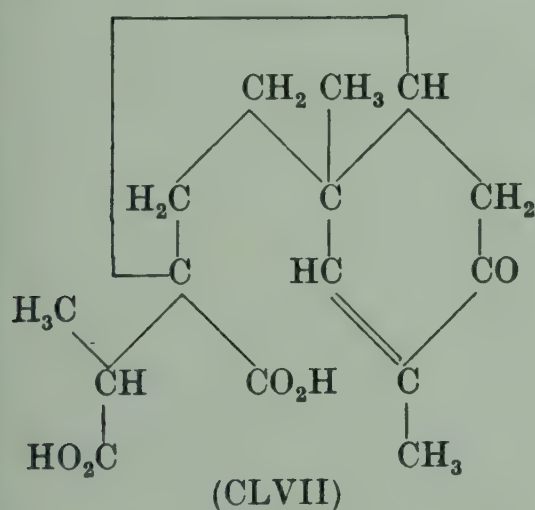


lactone (CLIV b), $C_{14}H_{20}O_4$, m.p. 193–194.5°, *acetate*, m.p. 160–163°. Similarly the diketo-lactone, obtained by chromic acid oxidation of aposantonic acid (p. 300) must be formulated (CLV) as a derivative of this hydroxy-lactone.

As was mentioned on p. 304, oxidation of metasantonic acid gives α -santoric acid. Metasantonic acid must therefore be simply a stereoisomer of santonic acid and can be represented by (CLVI).

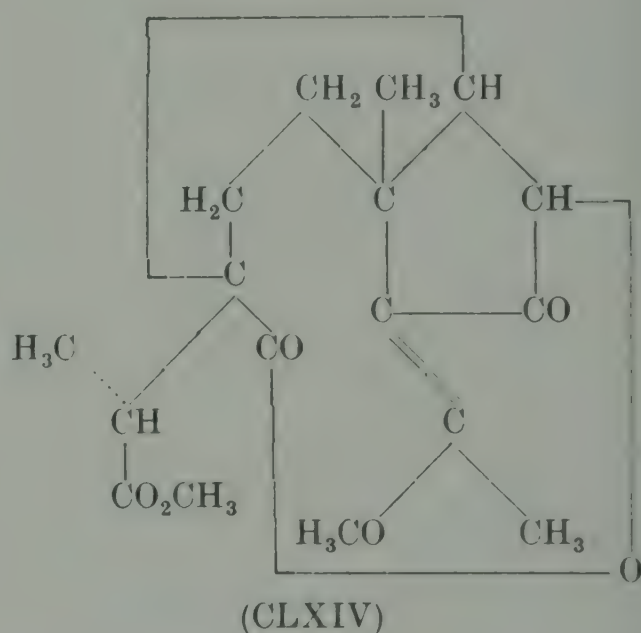
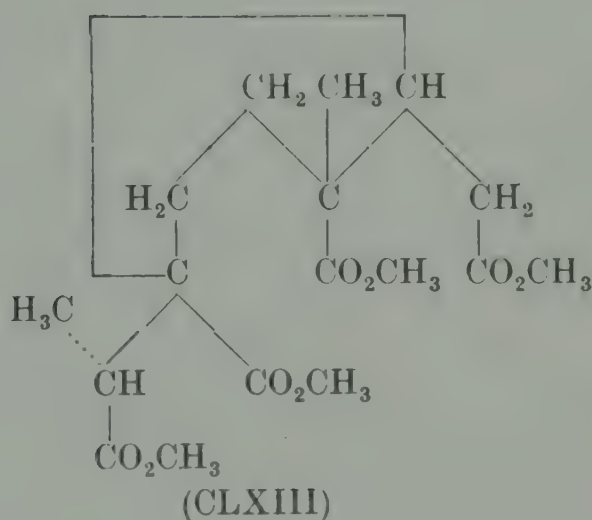
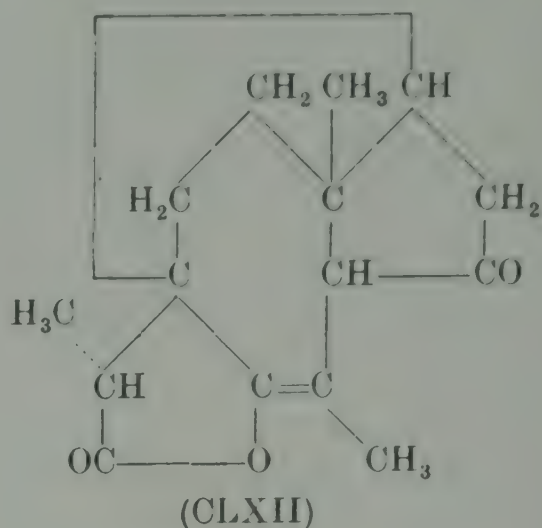
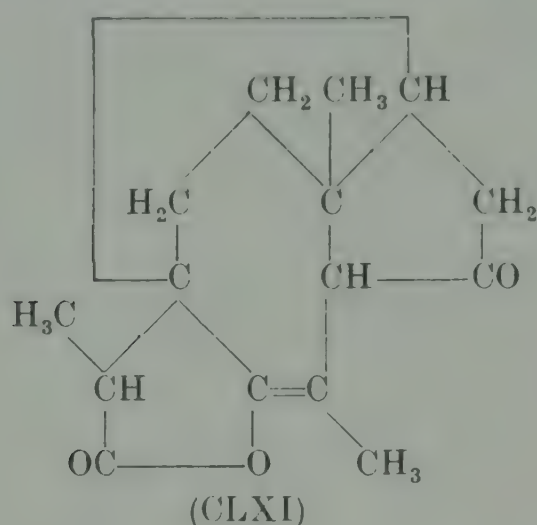


As a result of the investigations of Woodward, Brutschy and Baer* it is now possible to formulate various other derivatives



* *Loc. cit.*

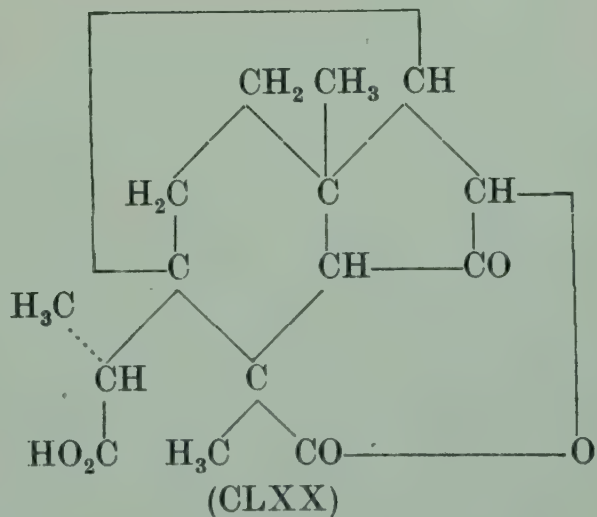
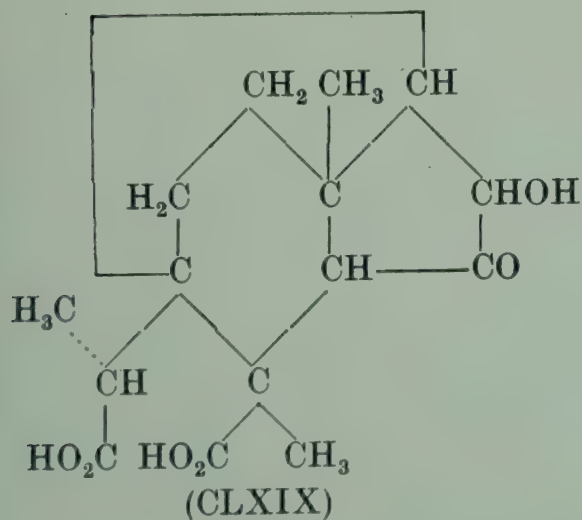
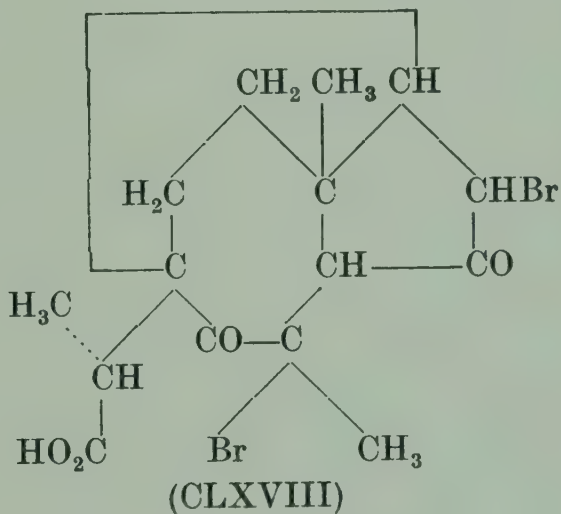
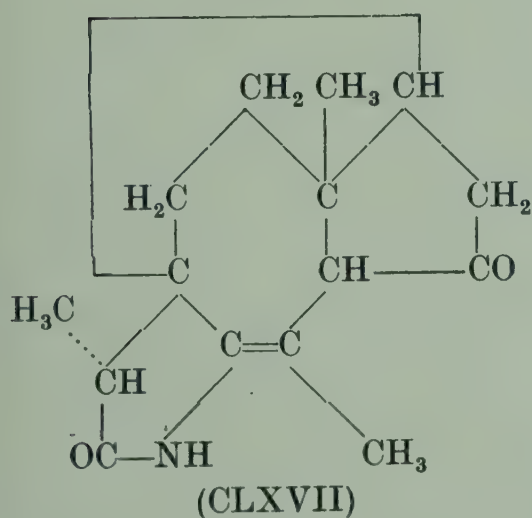
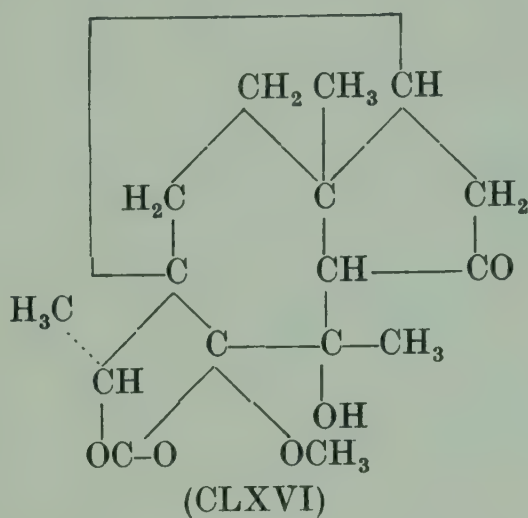
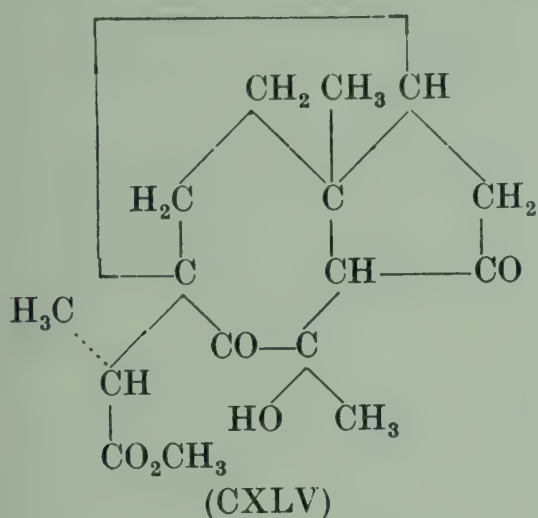
of santonic acid. Santolic acid (p. 301) must be formulated as (CLVII), hyposantonic acid (p. 301) as (CLVIII), the $C_{12}H_{16}O_2$ diketone from α -hydroxysantonin (p. 302) as (CLIX) and the derived dicarboxylic acid as (CLX).



Recently Woodward and Kovach* have suggested the constitutions (CLXI) for santonide and (CLXII) for parasantonide. These formulae are based mainly on the observation that ozonolysis of the latter lactone followed by treatment of the ozonide with methanolic hydrogen chloride afforded tetramethyl β -santorate, which may be written (see above) as (CLXIII), together with three other *compounds*, (CLXIV), $C_{17}H_{22}O_6$, m.p. 117° , (CLXV), $C_{16}H_{22}O_5$, m.p. 137° and (CLXVI), $C_{16}H_{22}O_5$, m.p. 155° . The constitutions assigned to the three last-mentioned substances are based mainly on a consideration of infra-red spectra and for details the original memoir

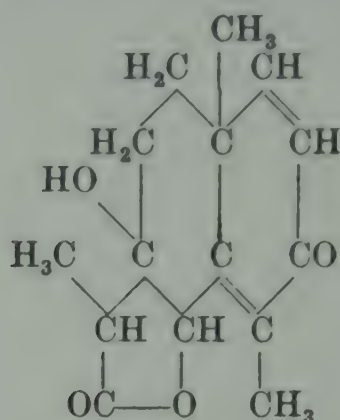
* *J. Amer. C.S.* 1950, **72**, 1009.

should be consulted. It is now possible to formulate in a plausible manner parasantonide imide as (CLXVII), dibromoparasantononic acid as (CLXVIII), dihydroxyparasantononic acid as (CLXIX) and dehydrodihydroxyparasantononic acid as (CLXX).^{*} In agreement with the formulation of santonide and parasantonide as stereoisomeric, it was found that methyl isosantonate and methyl parasantonate were equilibrated under the influence of sodium methoxide in methanol solution.

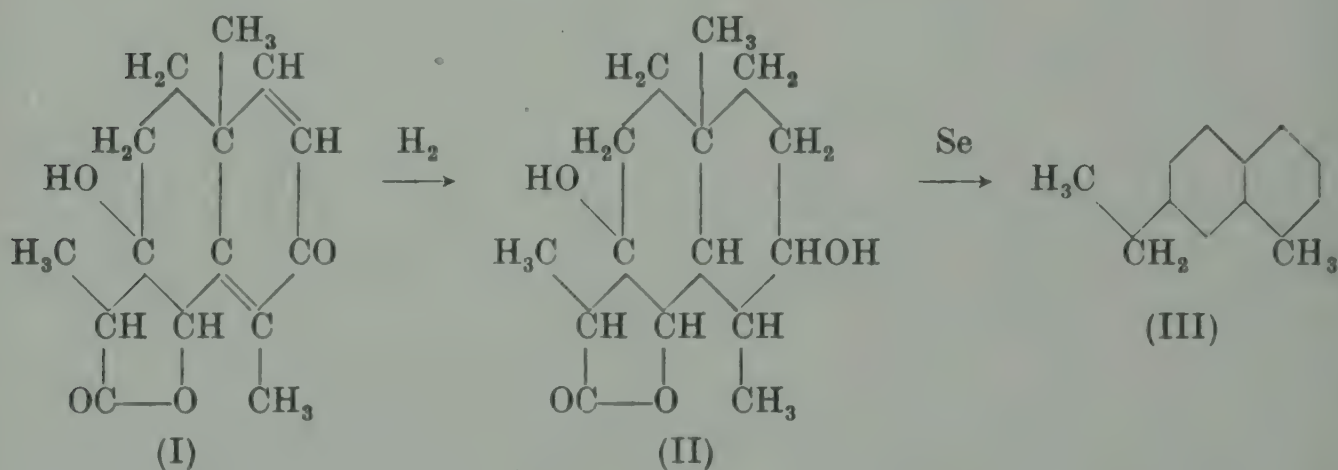


^{*} Woodward and Kovach, *loc. cit.*

ARTEMISIN (8-HYDROXYSANTONIN)



Artemisin was first isolated by Merck* in 1894 from the last mother liquors in the technical treatment of the seed of *Artemisia maritima*. It has been shown, principally by the investigations of Bertolo and of Tettweiler, Engel and Wedekind, to be an unsaturated hydroxy keto-lactone, $C_{15}H_{18}O_4$, closely related to santonin and possessing the formula (I). Artemisin has m.p. 203° , b.p. $260^\circ/0.1$ mm., $[\alpha]_D -84.3^\circ$ (in alcohol) and resembles santonin in its physiological effects.†



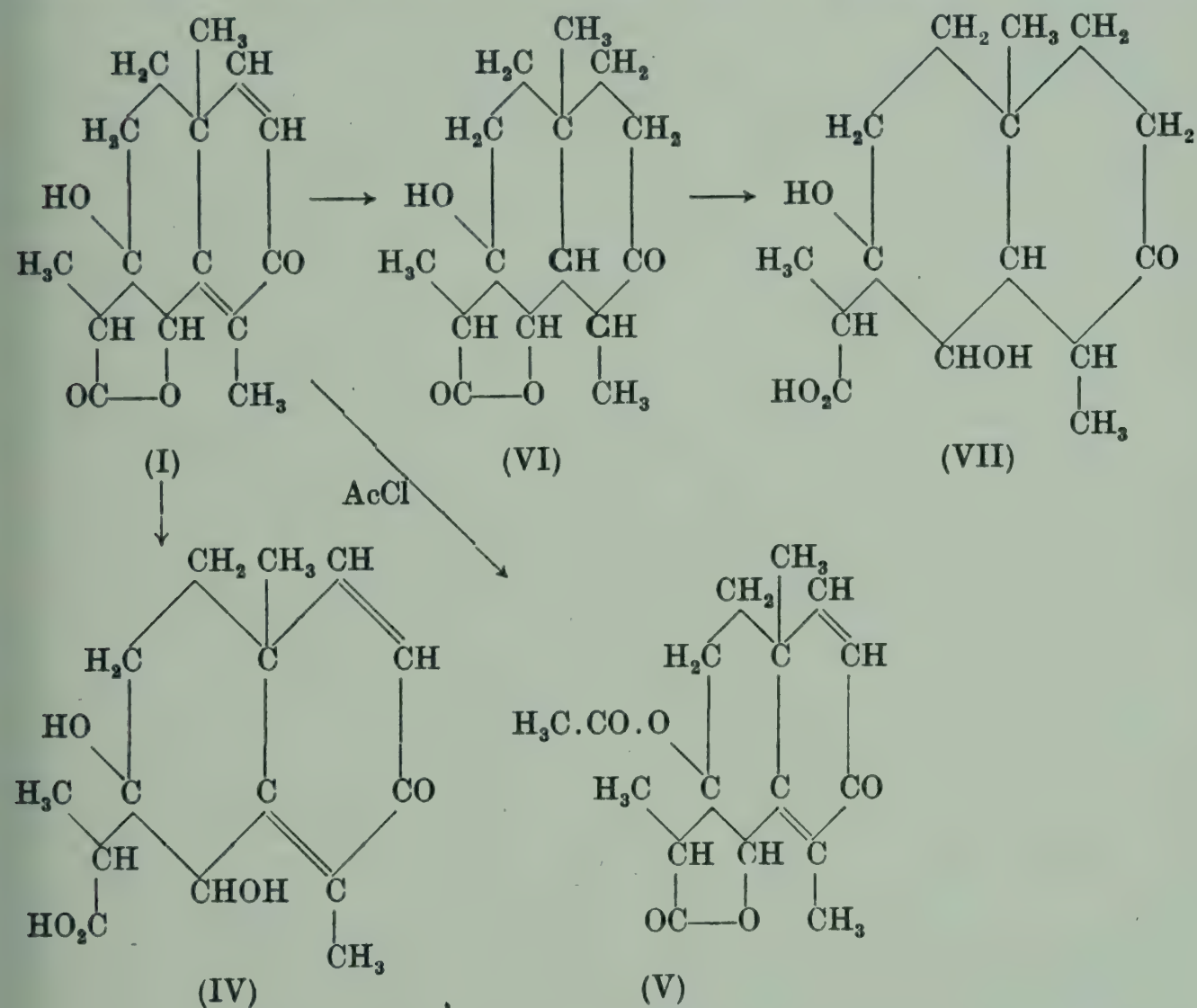
That artemisin belonged to the eudalene group of sesquiterpenes was shown by the following experiments bearing upon its carbon skeleton. When artemisin was catalytically hydrogenated with a platinum catalyst in acetic acid solution it afforded a mixture of two stereoisomeric *hexahydroartemisins*, $C_{15}H_{24}O_4$ (II), m.p.s 242° and 208° , which gave 1-methyl-7-ethylnaphthalene (III), b.p. $130-135^\circ/16$ mm., *picrate*, m.p. 96° ,

* Merck's *Jahresber.* 1894, p. 3.

† Compare Freund and Mai, *Ber.* 1901, **34**, 3717; Bertolo, *Gazz.* 1904, **34**, II, 322.

stypnate, m.p. 126°, on dehydrogenation with selenium.* This hydrocarbon has also been obtained from santonin, β -santonin, ψ -santonin and the alantolactones (see pp. 241, 259, 321, 322).

The functional groups present in artemisin have been characterised by the following observations. Artemisin is a lactone since, on warming with dilute alkalis, it forms salts of the corresponding hydroxy-acid, *artemisinic acid*, $C_{15}H_{20}O_5$ (IV), *methyl*



ester, m.p. 180°, and it can be regenerated unchanged by acidification of these solutions. The presence of a keto group was established by the preparation of a number of derivatives (see p. 319) and it contains also a tertiary hydroxyl group. It is acetylated only with difficulty to give *monoacetylartemisin*, $C_{17}H_{20}O_5$ (V), m.p. 200°, $[\alpha]_D^{25} - 52.6^\circ$ (in chloroform), *oxime*, m.p. 188–189°, *phenylhydrazone*, m.p. 145°.† The presence of two ethylenic linkages in artemisin has been shown by its catalytic hydrogena-

* Tettweiler, Engel and Wedekind, *Annalen*, 1932, 492, 105.

† Bertolo, *Gazz.* 1920, 50, I, 109; *Atti R. Accad. Lincei*, 1923 [v], 32, II, 76; *Gazz.* 1923, 53, 721; Tettweiler, Engel and Wedekind, *loc. cit.*

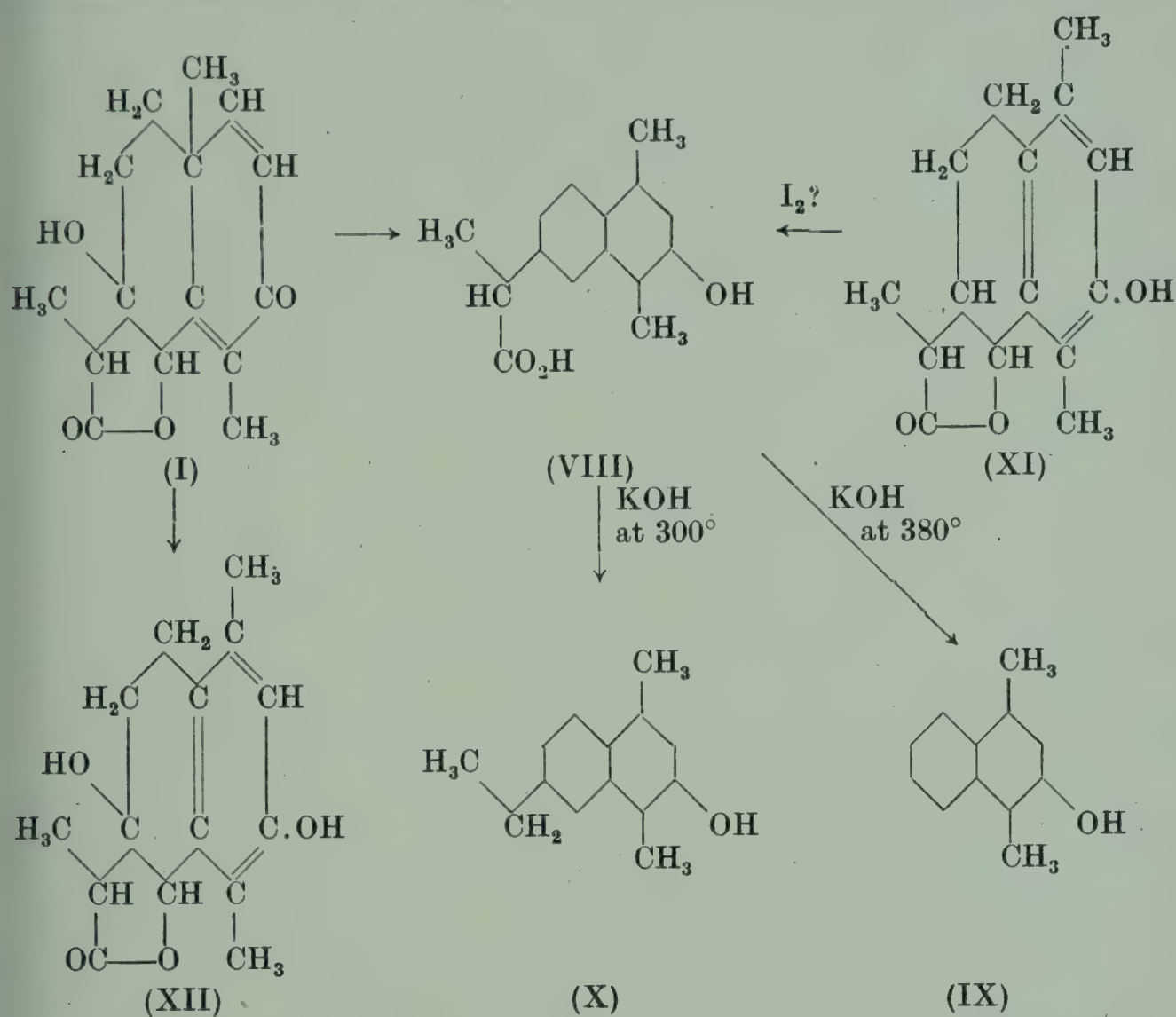
tion to a mixture of four saturated stereoisomeric *tetrahydroartemisins*, $C_{15}H_{22}O_4$ (VI), α -, m.p. 192° , $[\alpha]_D^{23} + 49.6^\circ$ (in alcohol), *oxime*, m.p. 248° decomp., *semicarbazone*, m.p. 245° decomp., β -, m.p. 169° , $[\alpha]_D^{23} + 65.2^\circ$ (in alcohol), *oxime*, m.p. 242° decomp., γ -, m.p. 224° , *oxime*, m.p. 256° decomp., δ -, m.p. 208° , *oxime*, m.p. 185° decomp., *oxime monohydrate*, m.p. 137° .^{*} These tetrahydroartemisins are lactones and give, by solution in alkali and acidification, the corresponding *tetrahydroartemisinic acid*, $C_{15}H_{24}O_5$ (VII), α -, decomp. 118° and β -, m.p. 218 – 220° decomp., which are considerably more stable than artemisinic acid itself (see above). The fact that four stereoisomeric tetrahydroartemisins have been reported has been taken to indicate that the hydrogenation of artemisin involves the creation of at least two asymmetric centres (shown in Clarendon type in (VI)), in agreement with the representation of artemisin as (I).

The position of the ketonic oxygen atom in the molecule of artemisin and an indication of its relationship with respect to the two ethylenic linkages has been demonstrated by the prolonged experiments of Bertolo.[†] On treatment with concentrated hydrochloric or sulphuric acids artemisin furnished by rearrangement and dehydration a phenolic acid, *artemismic acid*, $C_{15}H_{16}O_3$ (VIII), m.p. 135 – 136° , $[\alpha]_D + 70.4^\circ$ (in alcohol), *ethyl ester*, m.p. 97 – 98° , which on fusion with potassium hydroxide gave 1:4-*dimethyl-2-naphthol* (IX) (see also pp. 251, 264) or 1:4-*dimethyl-7-ethyl-2-naphthol* (X), m.p. 126° , *methyl ether*, m.p. 72° , depending upon the temperature at which the reaction was carried out. Substances which were very similar in properties to artemismic acid, but with lower melting-points, were obtained by the action of iodine on desmotroposantonin (XI) (see p. 315) and by the action of red phosphorus and hydriodic acid on artemisin. The resemblance between the formation of artemismic acid from artemisin, and of desmotroposantonin from santonin (see p. 257), indicated by these experiments was further supported by Bertolo's observation that artemisin, on treatment

^{*} Rimini and Jona, *Atti R. Accad. Lincei*, 1913 [v], **22**, II, 28; *Gazz.* 1913, **43**, II, 531; Tettweiler, Engel and Wedekind, *loc. cit.*; compare Bertolo, *Gazz.* 1908, **38**, 554.

[†] *Atti R. Accad. Lincei*, 1902 [v], **11**, I, 486; *ibid.* 1903 [v], **12**, II, 273; *Gazz.* 1920, **50**, I, 114; 1923, **53**, 867; 1926, **56**, 856; *Atti IV Congr. naz. chim. pura applicata* (1932), 1933, p. 396; compare *Atti R. Accad. Lincei*, 1923 [v], **32**, I, 486, 618; *Gazz.* 1923, **53**, 715, 724; *Atti R. Accad. Lincei*, 1925 [vi], **1**, 127, 436.

with dilute sulphuric acid at temperatures less than 60° , afforded, by rearrangement, an isomeric phenolic lactone, *desmotropoartemisin*, $C_{15}H_{18}O_4$ (XII), m.p. 236° , $[\alpha]_D^{27^\circ} - 84.2^\circ$ (in alcohol), *acetate*, m.p. $154-155^\circ$, $[\alpha]_D^{30^\circ} - 66.9^\circ$ (in alcohol), *diacetate*, m.p. $149-150^\circ$, $[\alpha]_D^{25^\circ} - 50.8^\circ$ (in alcohol). Bertolo also

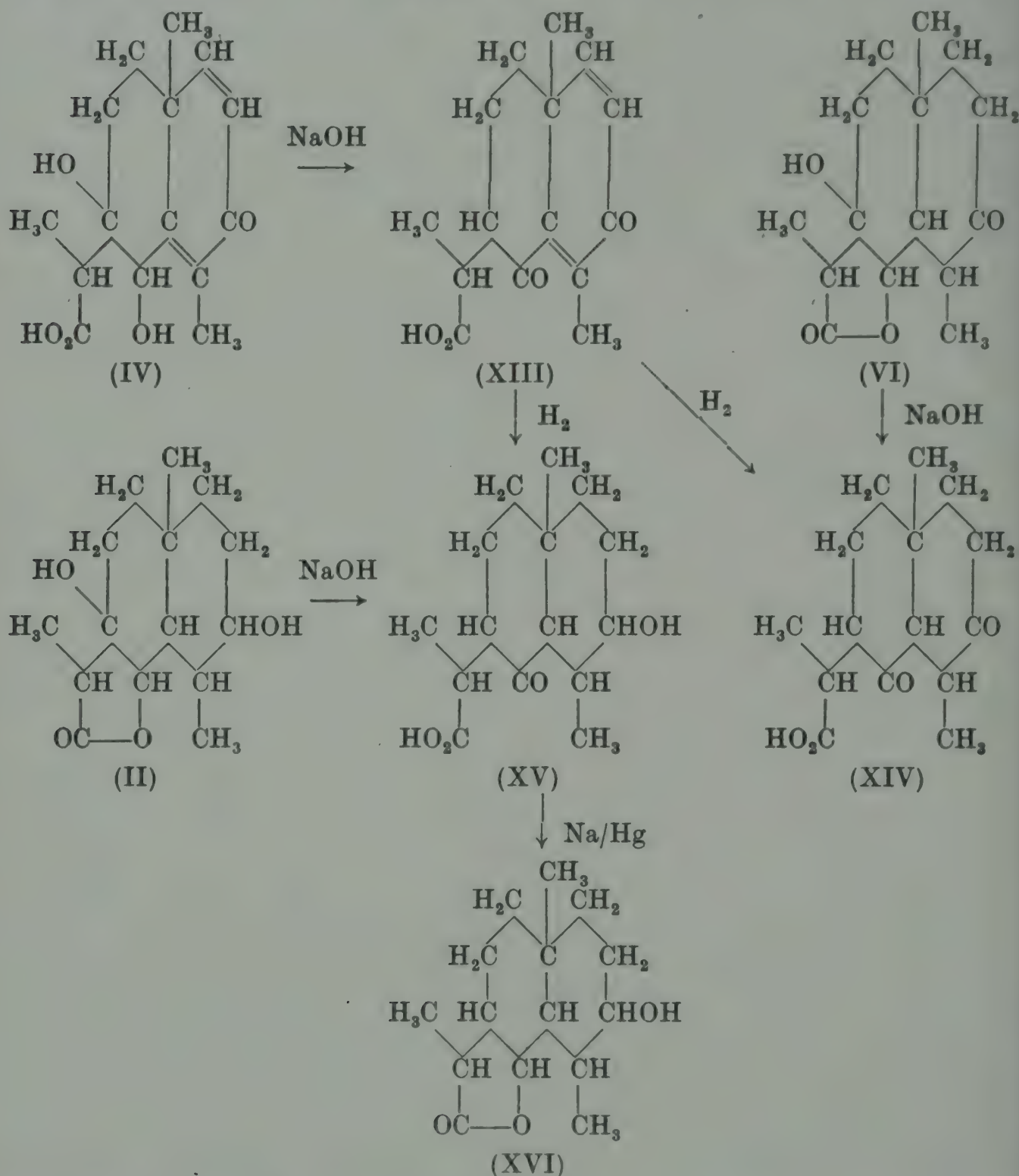


found that artemisin was reduced by stannous chloride in hydrochloric acid solution to a *substance*, $C_{15}H_{18}O_3$, m.p. $269-270^\circ$, *acetate*, m.p. $205-206^\circ$, which may be a stereoisomer of desmotroposantonin (XI) (see p. 265) and which, like desmotroposantonin, afforded 1:4-dimethyl-2-naphthol (IX), on fusion with potassium hydroxide.

Although Bertolo had provisionally assigned the tertiary hydroxyl group of artemisin to the β -position with respect to the carboxyl of the lactone grouping, proof of the correctness of this view was finally provided by the experiments of Tettweiler, Engel and Wedekind.* The results of these investigators are

* *Annalen*, 1932, **492**, 105; compare Bertolo, *Atti R. Accad. Lincei*, 1923 [v], **32**, I, 486, 618; *Gazz.* 1920, **50**, I, 109; 1923, **53**, 721, 867.

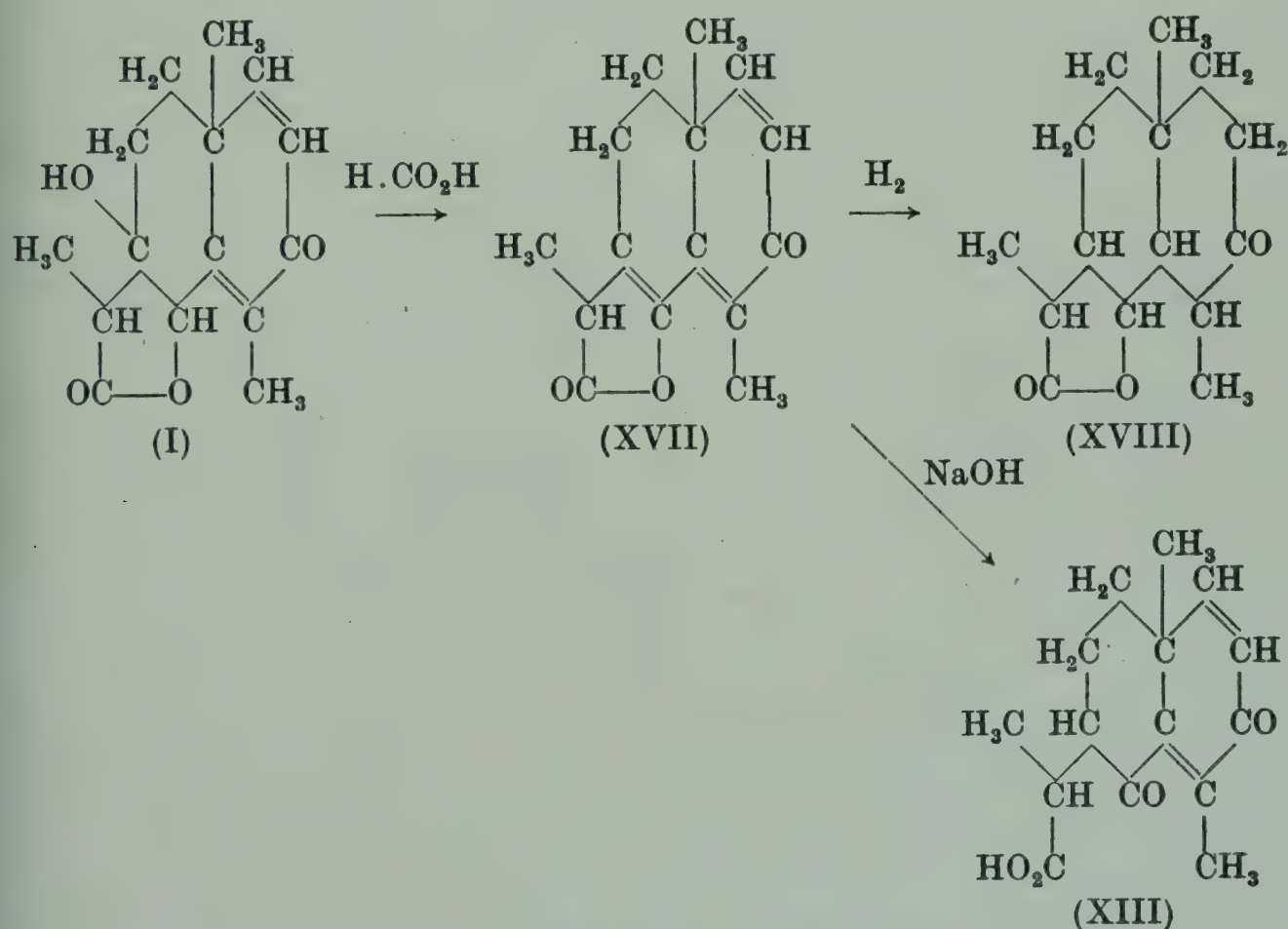
summarised below. On boiling with a 10 per cent. solution of sodium hydroxide artemisinic acid (IV) was dehydrated to a diketo-acid, *artemionic acid*, $C_{15}H_{18}O_4$ (XIII), m.p. 208° , *methyl ester*, m.p. 160° , which afforded the saturated diketo-acid, *tetrahydroartemionic acid*, $C_{15}H_{22}O_4$ (XIV), m.p. 192° , on catalytic



hydrogenation. Tetrahydroartemionic acid was also formed from α -tetrahydroartemisin (VI) by a similar alkaline treatment. Hydrogenation of artemionic acid in the presence of a more active catalyst afforded *hexahydroartemionic acid*, $C_{15}H_{24}O_4$ (XV), m.p. 179° , which was also obtained by alkaline treatment of the mixed

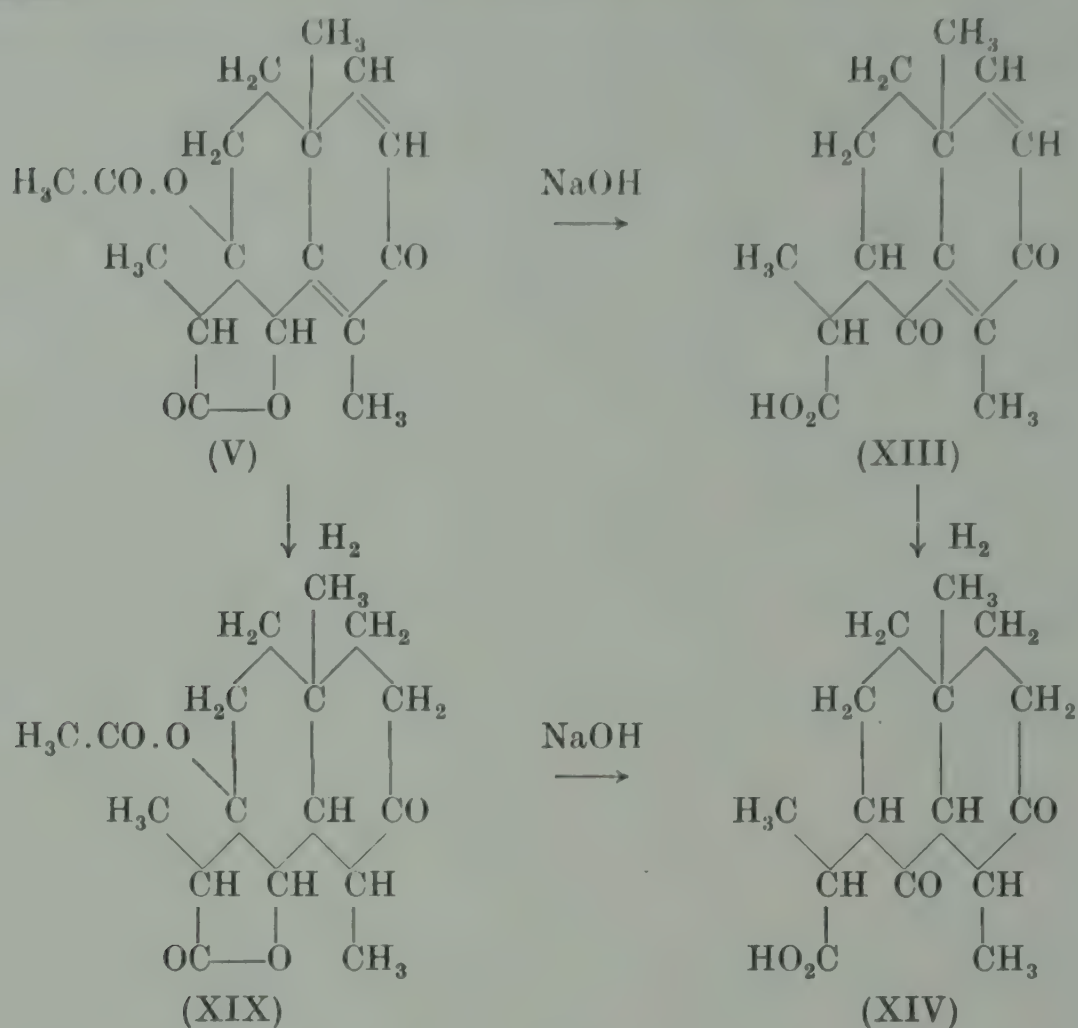
hexahydroartemisins (II). Hexahydroartemionic acid, although resistant to further catalytic hydrogenation, was readily reduced by sodium amalgam to hexahydrosantonin (XVI) (see p. 260), thus proving the position of fusion of the lactonic ring in artemisin to be the same as that in santonin. These reactions can best be formulated if the tertiary hydroxyl group of artemisin is in the 8 position as indicated in the scheme set out on p. 316.

Further confirmation of the position of the tertiary hydroxyl group in artemisin was obtained in the following way. When artemisin was heated with formic acid it was dehydrated to the unsaturated lactone, *artemisene*, $C_{15}H_{16}O_3$ (XVII), m.p. 182° , *oxime*, m.p. $244-245^\circ$ decomp., which was readily hydrogenated to the saturated lactone, *hexahydroartemisene*, $C_{15}H_{22}O_3$ (XVIII), m.p. 199° . On mild treatment with sodium hydroxide artemisene gave artemionic acid (XIII), the formation of which is most readily explained if the original hydroxyl group of artemisin be in the 8 position.



Artemionic acid was also formed by the alkaline hydrolysis of acetylartemisin (V), whilst tetrahydroartemionic acid (XIV), was similarly obtained by alkaline hydrolysis of *acetyltetrahydroartemisin*, $C_{17}H_{24}O_5$ (XIX), m.p. 166° , *oxime*, m.p. 139° decomp.

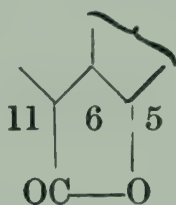
This latter substance can be prepared by direct acetylation of α -tetrahydroartemisin or by catalytic hydrogenation of acetyl-artemisin.



The stereochemistry of artemisin relative to santonin and its derivatives (see p. 268) has been discussed by Barton.* The rotation of artemisic acid $[\alpha]_D + 70.4^\circ$ (in alcohol) is clearly analogous to that of santinic acid $[\alpha]_D + 64.4^\circ$ (in alcohol) (see p. 253), and implies that the configuration of artemisin at C_{11} must be (*d*) as in santonin. Now the conversion of artemisin to artemisone and isoartemisone (see below) is comparable to the conversion of santonin to santonone and isosantonone (p. 273) and implies a similarity in stereochemistry. This means that the lactone ring fusion in artemisin must be *trans* as in santonin and β -santonin (see p. 268). Undoubtedly desmotropoartemisin is analogous to the desmotroposantonins in having its lactone ring *cis* fused. Assuming that the substitution of a hydroxyl group for a hydrogen atom does not alter the sign of the molecular rotation contribution of an asymmetric centre possessing a particular spatial configuration, then reference to the isomeric desmotropo-

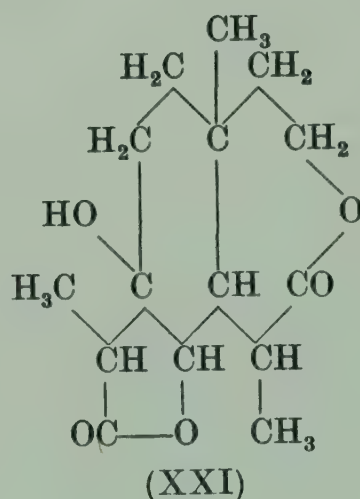
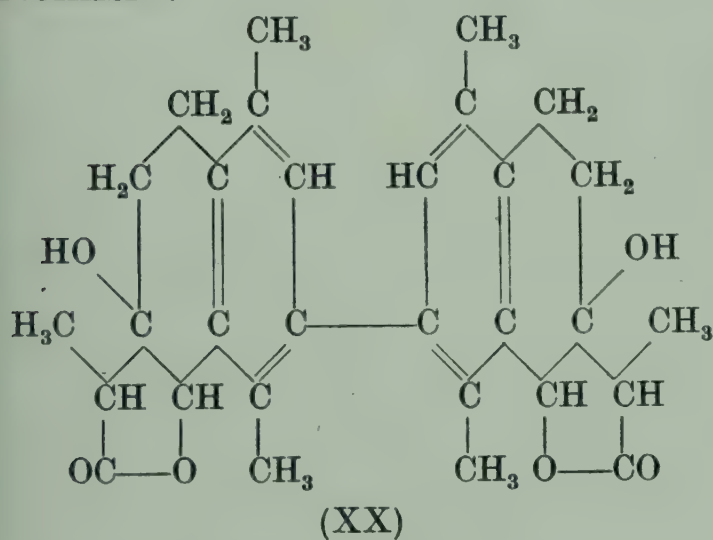
* *J. Org. Chem.* 1950, 15, 466.

santonins (p. 265) shows that desmotropoartemisin must be analogous to *l*-desmotroposantonin and must therefore be formulated as $C_5(l):C_6(d):C_{11}(d)$. Since the conversion of artemisin to desmotropoartemisin cannot involve a change at C_6 , artemisin must be $C_5(d):C_6(d):C_{11}(d)$ and, for the same reason as with santonin (see p. 269), $C_9(l)$.



Artemisin can be characterised by the formation of an *oxime*, m.p. 233–234°, and a *phenylhydrazone*, m.p. 144–145° (rapid heating) or m.p. 221–222° (slow heating), $[\alpha]_D^{24} + 180^\circ$.^{*} Artemisin also forms a characteristic chloroform addition compound, $C_{15}H_{18}O_4$, $CHCl_3$, which decomposes at 80°.

The action of alkaline potassium permanganate on artemisin has been studied by Horst[†] and by Rimini,[‡] but it is impossible to reconcile their results with the formula now accepted for artemisin.



On reduction with zinc dust and 50 per cent. aqueous acetic acid artemisin is converted to a dilactone *artemisone*, $C_{30}H_{34}O_6$, m.p. 273–274°, $[\alpha]_D^{18.5} + 159^\circ$ (in acetic acid), which by analogy with santonone (see p. 274) should doubtless be formulated as (XX). On acidification of alkaline solutions of artemisone an isomeric substance, *isoartemisone*, m.p. 182–183°, $[\alpha]_D^{19.5} - 157^\circ$

^{*} Bertolo, *Atti R. Accad. Lincei*, 1901 [v], 10, II, 111; *Gazz.* 1911, 41, I, 705.

[†] *Chem. Ztg.*, 26, 203.

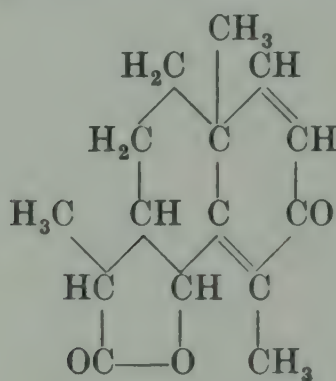
[‡] *Atti R. Accad. Lincei*, 1908 [v], 17, II, 590.

(in alcohol), $[\alpha]_D^{13} - 153^\circ$ (in acetic acid) is obtained, which is presumably analogous to *isosantonone* (see p. 273). In agreement with this view *isoartemisone* is best prepared by zinc dust reduction of artemisin using 70–80 per cent. aqueous acetic acid. Artemisone and *isoartemisone* are not enantiomorphous* and undoubtedly differ from each other in having respectively a *trans* and *cis* fusion of the lactone rings.†

Ill-defined halogen derivatives of artemisin have been described by Rimini and Jona‡ and by Bertolo.§

When α -tetrahydroartemisin is oxidised with Caro's acid it gives a *dilactone*, $C_{15}H_{22}O_5$, m.p. 224° decomp., which can be formulated as (XXI). The formation of this substance is analogous to the action of Caro's acid on tetrahydrosantonin (see p. 280).||

β -SANTONIN



β -Santonin, $C_{15}H_{18}O_3$, m.p. 216 – 218° , $[\alpha]_D^{19} - 137.2^\circ$ (in chloroform), occurs together with santonin in samples of *Artemisia* obtained from the North-West Frontier of India. It has been shown by Clemo¶ to be a stereoisomeride of *l*-santonin (see p. 249) which it closely resembles in its colour reactions.

It was observed by Clemo that when β -santonin (I) was treated with either dilute sulphuric acid or hydrochloric acid it was isomerised to *l*-desmotropo- β -santonin (II), m.p. 253° , $[\alpha]_D - 101.7^\circ$ (in ethyl acetate), *acetate*, m.p. 156 – 157° , which gave on reduction with zinc dust and acetic acid *d*- β -santonous acid, $C_{15}H_{20}O_3$ (III), m.p. 174° , $[\alpha]_D + 54.9^\circ$ (in alcohol). If, however,

* Bertolo and Ranfaldi, *Gazz.* 1905, **35**, II, 235.

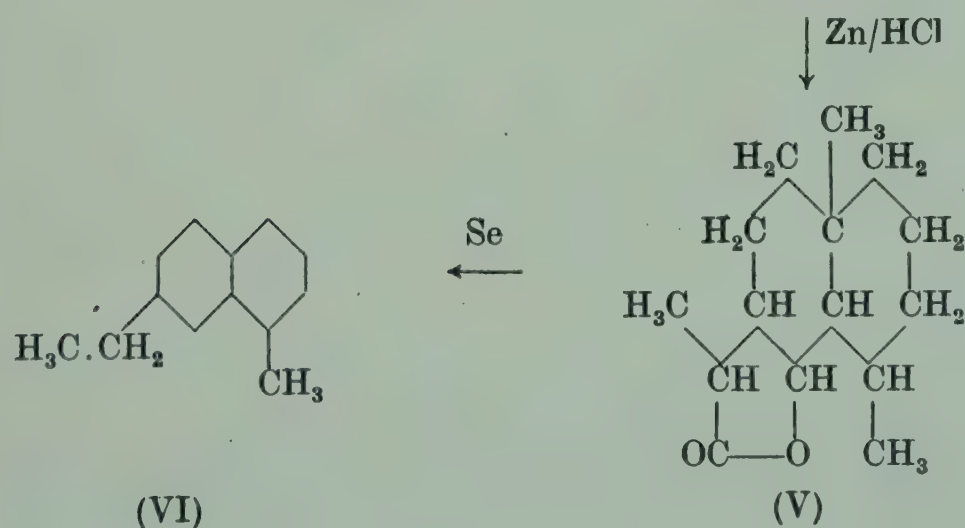
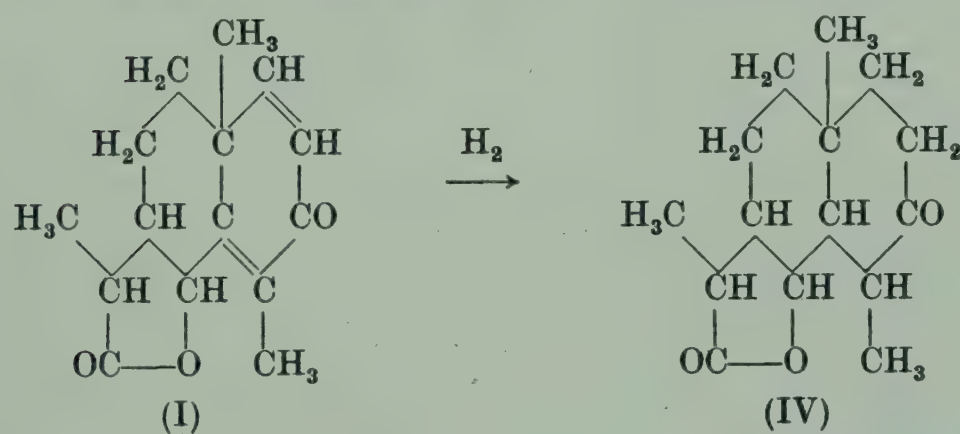
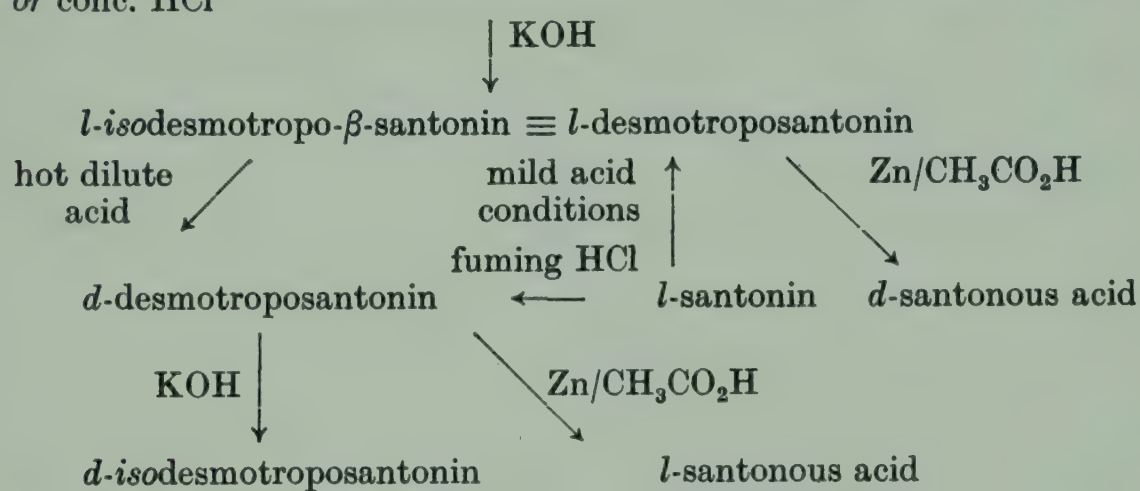
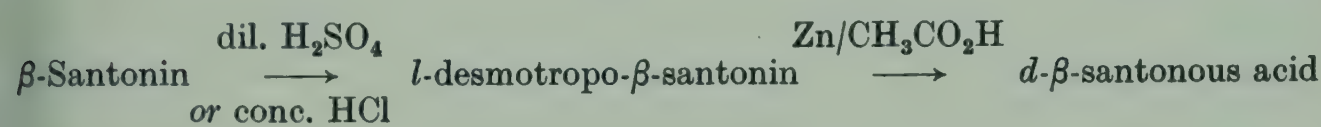
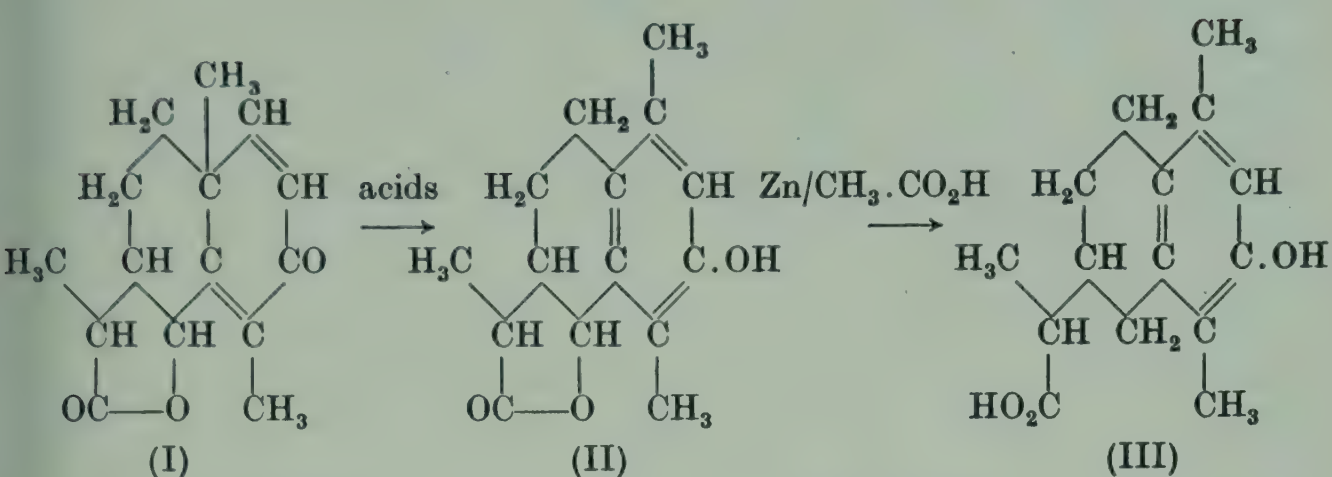
† Compare Barton, *loc. cit.*

‡ *Atti R. Accad. Lincei*, 1913 [v], **22**, II, 71; *Gazz.* 1913, **43**, II, 531.

§ *Gazz.* 1920, **50**, I, 109.

|| Tettweiler, Engel and Wedekind, *Annalen*, 1932, **492**, 105.

¶ *J.C.S.* 1934, p. 1343.



l-desmotropo- β -santonin was heated at 210° with potassium hydroxide it was converted into *l*-isodesmotropo- β -santonin, which was found to be identical with *l*-desmotroposantonin (see p. 264). The relationship between β -santonin and *l*-santonin, which is illustrated in the scheme on p. 321, must be of a stereochemical nature.*

On catalytic hydrogenation β -santonin was converted to a mixture of two *tetrahydro- β -santonins*, $C_{15}H_{22}O_3$ (IV), (a) m.p. 207–208°, and (b) m.p. 125–126°. Both these *tetrahydro- β -santonins*, on reduction by the Clemmensen method, afforded the same *deoxytetrahydro- β -santonin*, $C_{15}H_{24}O_2$ (V), m.p. 75–76°, from which *1-methyl-7-ethylnaphthalene* (VI), was obtained on dehydrogenation with selenium.

β -Santonin can be most readily characterised by the preparation of its *oxime*, m.p. 224°.

ψ -SANTONIN

In addition to *l*-santonin, β -santonin and artemisin, the flower heads of *Artemisia maritima* have been found by Clemo and Cocker† to contain, in small amount, a hydroxy keto-lactone, ψ -santonin, $C_{15}H_{20}O_4$, m.p. 183–184°, $[\alpha]_D^{20} - 169^\circ$ (in chloroform).

The chemistry of ψ -santonin has been extensively investigated by Cocker and his collaborators.‡

The presence in ψ -santonin of the same ring system as that in santonin and that it was an unsaturated lactone containing a carbonyl group and a hydroxy group was readily demonstrated. It was insoluble in cold alkali, but dissolved readily on warming, being reprecipitated unchanged on acidification. On hydrogenation with a palladised charcoal catalyst an unsaturated acid, *dihydro- ψ -santonin*, $C_{15}H_{22}O_4$, m.p. 188–189°, $[\alpha]_D^{20} - 239^\circ$ (in acetic acid), *methyl ester*, m.p. 77°, *oxime*, m.p. 229–230°, was obtained.

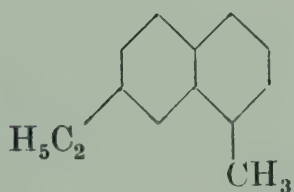
* For a fuller discussion of this and other points of stereochemistry see p. 267.

† *J.C.S.* 1946, p. 30.

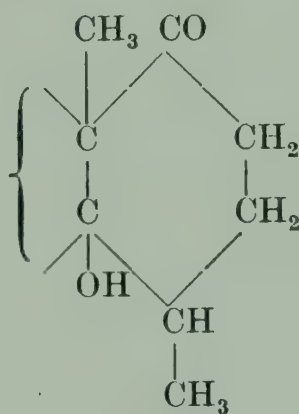
‡ Clemo and Cocker, *loc. cit.*; Cocker, *J.C.S.* 1946, p. 36; Cocker and Lipman, *ibid.* 1947, p. 533; Cocker and Hornsby, *ibid.* p. 1157; Cocker, Cross and Lipman, *ibid.* 1949, pp. 959, 1170; Cocker *et al.*, *ibid.* 1950, p. 1781; see also Cocker, Lipman and Whyte, *ibid.* 1950, p. 1519.

Reduction of dihydro- ψ -santonin by the Clemmensen method followed by dehydrogenation of the product with selenium afforded 1-methyl-7-ethylnaphthalene (I), a hydrocarbon previously obtained by dehydrogenation of santonin and artemisin (see pp. 259, 312). The formation of this hydrocarbon proves the position of one methyl group and, from analogy with santonin, that of the lactone ring. The methyl group eliminated during the dehydrogenation must, on the basis of the isoprene rule, be in position 9.

The presence of the carbonyl group in ψ -santonin was proved by the formation of an *oxime*, m.p. 203–204°. That there was a methylene group in the α -position to the keto-group was shown by reaction with *o*-aminobenzaldehyde which afforded a *quinoline* derivative, $C_{22}H_{23}O_3N$, m.p. 210°. The carbonyl group is most probably situated as in the formula (II) as shown by the following evidence. By the action of 55 per cent sulphuric acid



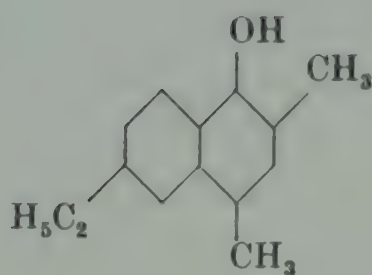
(I)



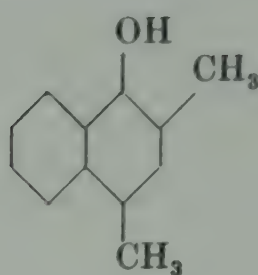
(II)

or formic acid on ψ -santonin, the phenolic lactone *d*- β -desmotropo- ψ -santonin,* $C_{15}H_{18}O_3$, m.p. 185–186°, $[\alpha]_D^{20} + 67.9^\circ$ (in chloroform), *acetate*, m.p. 233°, *benzoate*, m.p. 164°, *methyl ether*, m.p. 159–160°, $[\alpha]_D^{18} + 61.3^\circ$ (in acetic acid), *carbanilate*, m.p. 222–223°, was formed. On careful palladised charcoal dehydrogenation this furnished what is almost certainly 2:4-dimethyl-6-ethylnaphth-1-ol (III), $C_{14}H_{16}O$, m.p. 113°; *carbanilate*, m.p. 150–151°, *picrate*, m.p. 143–144°, trinitrobenzene *adduct*, m.p. 150–151°, whilst by fusion with potassium hydroxide it gave 2:4-dimethylnaphth-1-ol (IV), m.p. 81–82°, *carbanilate*, m.p. 174–175°, *picrate*, m.p. 143–144°. *d*- β -Desmotropo- ψ -santonin should, therefore, be represented by (V).

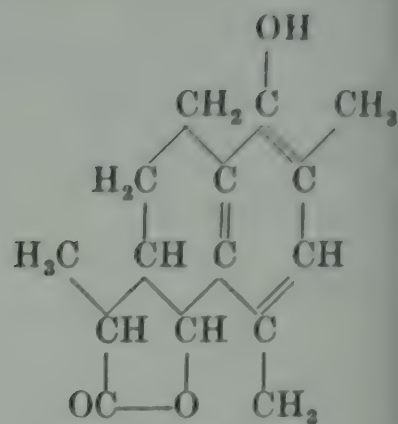
* For note on nomenclature, see p. 264.



(III)

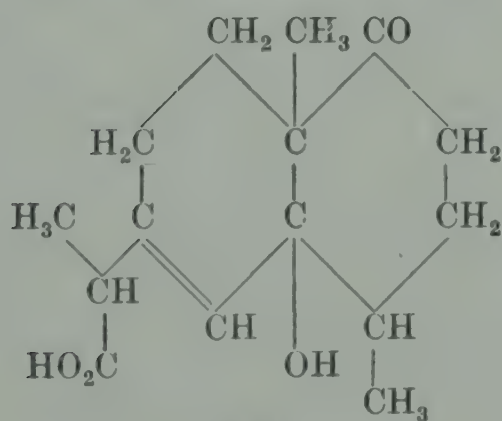


(IV)

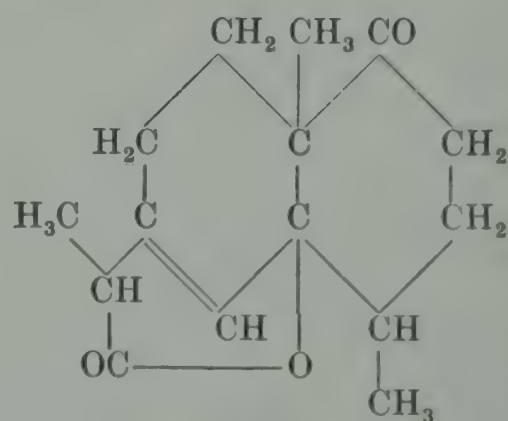


(V)

The hydroxyl group in ψ -santonin is probably tertiary, since it is only acetylated with difficulty to give in poor yield an *acetyl* derivative, $C_{17}H_{22}O_5$, m.p. 187° , $[\alpha]_D^{20} - 69.2^\circ$ (in chloroform), *oxime*, m.p. $196-197^\circ$, which did not regenerate ψ -santonin on hydrolysis, but instead a new isomeric *lactone*, m.p. $205-207^\circ$. It was suggested that this hydroxyl group is situated as in part formula (II), since when dihydro- ψ -santonin, for which formula (VI) has been considered, was heated with acetic anhydride a *lactone*, $C_{15}H_{20}O_3$, m.p. 158° , *oxime*, m.p. 188° , was obtained. This substance is much less resistant to hydrolytic reagents than ψ -santonin and formula (VII) has been suggested as a possible representation. Support for this formulation was provided by the observation that on treatment with hydroxylamine a *hydroxamic acid*, $C_{15}H_{24}O_4N_2$, m.p. $209-210^\circ$, was formed, a reaction fairly characteristic for δ -lactones.



(VI)

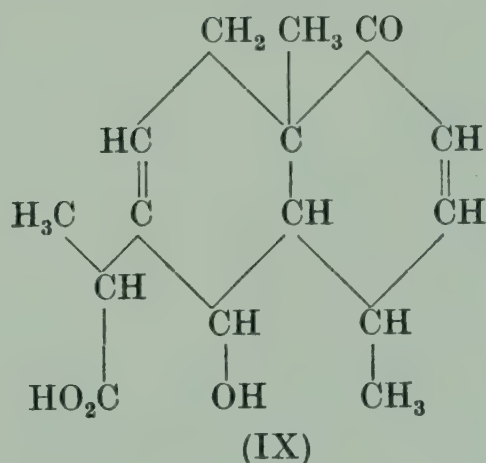
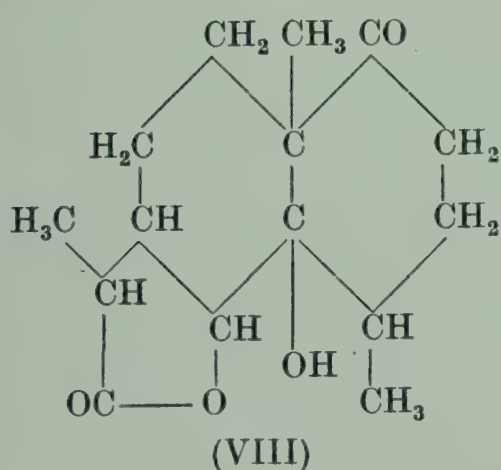


(VII)

It was concluded from the reactions summarised above that ψ -santonin is probably represented by (VIII) with an ethylenic linkage in the $\alpha:\beta$ - or one of the $\beta:\gamma$ -positions with respect to the lactonic carbonyl group. The evidence on this latter point is in conflict and the reader is referred to the original memoirs for more detailed discussion.

The conversion of ψ -santonin to d - β -desmotropo- ψ -santonin under the influence of acidic reagents was mentioned briefly above. An additional stereoisomer, d - α -isodesmotropo- ψ -santonin, m.p. 251–253°, $[\alpha]_D^{20} + 68.5^\circ$ (in alcohol), *acetate*, m.p. 244.5–245.5°, $[\alpha]_D^{20} + 64.1^\circ$ (in chloroform), is formed in minor amount at the same time. On heating with potassium carbonate in xylene solution d - β -desmotropo- ψ -santonin was isomerised to d - α -desmotropo- ψ -santonin, m.p. 171–172°, $[\alpha]_D^{20} + 155^\circ$ (in chloroform), *acetate*, m.p. 214°, $[\alpha]_D^{18} + 121^\circ$ (in chloroform), *methyl ether*, m.p. 150°, and similarly d - α -isodesmotropo- ψ -santonin was isomerised to d - β -isodesmotropo- ψ -santonin, m.p. 268–270°, $[\alpha]_D^{18} + 165^\circ$ (in chloroform), *acetate*, m.p. 223–224°, $[\alpha]_D^{14} + 135^\circ$ (in chloroform). These reactions in the ψ -santonin series parallel the reactions of the structurally analogous desmotroposantonins in the santonin series (see p. 264).

d - β -Desmotropo- ψ -santonin is not the first product of the action of acid on ψ -santonin, for under milder conditions a substance called ψ -santoninic acid, $C_{15}H_{20}O_4$, H_2O , m.p. 175–176°, $[\alpha]_D^{16} + 65.4^\circ$ (in alcohol), 2:4-dinitrophenylhydrazone, m.p. 193–194°, is formed. Formula (IX) has been tentatively suggested for ψ -santoninic acid, and it is in agreement with the spectroscopic



properties of the acid and also with the reactions described in the sequel. On treatment with perbenzoic acid a lactonic *dioxide*, $C_{15}H_{20}O_6$, m.p. 265–266°, $[\alpha]_D^{12} - 45.9^\circ$ (in alcohol), was formed. Hydrogenation using a palladised charcoal catalyst afforded *tetrahydro- ψ -santoninic acid*, m.p. 197–198°, $[\alpha]_D^{23} + 52^\circ$ (in alcohol), *oxime*, m.p. 230° decomp., *methyl ether*, m.p. 68–69°, *o*-aminobenzaldehyde condensation *product*, $C_{22}H_{27}O_3N$, m.p. 212–213°, whereas hydrogenation using a platinum catalyst gave

a *hexahydro-derivative*, $C_{15}H_{26}O_4$, m.p. 185° , lactonic *acetate* m.p. $120-121^\circ$. On heating ψ -santonin acid at 200° for a few minutes the corresponding lactone, *anhydro- ψ -santonin acid*, $C_{15}H_{18}O_3$, m.p. $191-192^\circ$, $[\alpha]_D^{19^\circ} + 110^\circ$ (in chloroform), was formed, which gave a *tetrahydro derivative*, m.p. $119-120^\circ$, $[\alpha]_D^{19^\circ} + 10.2^\circ$ (in alcohol), 2:4-*dinitrophenylhydrazone*, m.p. $220-221^\circ$. Similarly hexahydro- ψ -santonin acid (see above) gave *anhydrohexahydro- ψ -santonin acid*, $C_{15}H_{24}O_3$, m.p. $150-152^\circ$.

On treatment with acetic anhydride tetrahydro- ψ -santonin acid furnished α -anhydrotetrahydro- ψ -santonin acid, $C_{15}H_{22}O_3$, m.p. $147-148^\circ$, $[\alpha]_D^{21^\circ} - 133^\circ$ (in alcohol), 2:4-*dinitrophenylhydrazone*, m.p. 210° decomp. The action of heat on tetrahydro- ψ -santonin acid gave a further isomer, β -anhydrotetrahydro- ψ -santonin acid, m.p. $159-160^\circ$, which was also formed by rearrangement of the α -isomer by attempted hydrogenation. On heating with caustic alkali both α - and β -compounds afforded an acid, $C_{15}H_{24}O_4$, H_2O , m.p. $205-206^\circ$, $[\alpha]_D^{19^\circ} + 103.3^\circ$ (in alcohol).

On Clemmensen reduction followed by dehydrogenation, tetrahydro- ψ -santonin acid gave 1-methyl-7-ethylnaphthalene (I).

ψ -Santonin furnished a saturated *oxide*, $C_{15}H_{20}O_5$, m.p. $145.5-146.5^\circ$, 2:4-*dinitrophenylhydrazone*, m.p. $238-240^\circ$, on treatment with perbenzoic acid.

The action of degradative oxidising agents on ψ -santonin does not appear to have been investigated. As mentioned above it gives on further catalytic hydrogenation dihydro- ψ -santonin. This can be further reduced by treatment with sodium amalgam to a glycol, $C_{15}H_{24}O_4$, m.p. $189-190^\circ$, which was converted by the action of acetic anhydride into its acetylated *lactone*, $C_{17}H_{24}O_4$, m.p. 104° .

Using a platinum catalyst dihydro- ψ -santonin was hydrogenated to *hexahydro- ψ -santonin*, $C_{15}H_{26}O_4$, m.p. $191-192^\circ$, from which the corresponding acetylated *lactone*, $C_{17}H_{26}O_4$, m.p. 125° , was similarly prepared by the action of acetic anhydride. Hexahydro- ψ -santonin was also prepared by the hydrogenation of tetrahydro- ψ -santonin using a platinum catalyst.

With bromine, depending upon the conditions used, ψ -santonin furnished a *monobromo-derivative*, $C_{15}H_{19}O_4Br$, m.p. $198-199^\circ$, *oxime*, m.p. 251° decomp., or a *tribromo-derivative*, $C_{15}H_{19}O_4Br_3$, m.p. 243° . The monobromo- ψ -santonin could also be prepared

from the tribromo-compound by catalytic hydrogenation with a palladised charcoal catalyst. Both these substances regenerated ψ -santonin on treatment with zinc in alcoholic solution.

With bromine in sodium carbonate solution dihydro- ψ -santonin furnished a *bromo-lactone*, $C_{15}H_{21}O_4Br$, m.p. 180° , which regenerated dihydro- ψ -santonin on reduction with zinc in alcoholic solution.

ψ -Santonin can be readily characterised by the preparation of its oxime (see above) and of a 2:4-*dinitrophenylhydrazone*, m.p. 257° . It resembles digitalis in its cardiac effect on the frog's heart. A report of its pharmacological properties has been made by Baldwin.*

* *Pharm. J.* 1943, 151, 22.

PART II

THE DITERPENES AND THEIR DERIVATIVES

INTRODUCTION

The name diterpene should, strictly speaking, be applied only to the hydrocarbon constituents of essential oils which have the composition $C_{20}H_{32}$. Diterpene hydrocarbons occur but rarely in nature and the most important and abundant of diterpene derivatives (*diterpenoids*) are the carboxylic acids of which abietic acid, *d*-pimaric acid and levopimaric acid are the most important. Alcohols, oxides and other oxygenated derivatives of the diterpenes are also found in nature.

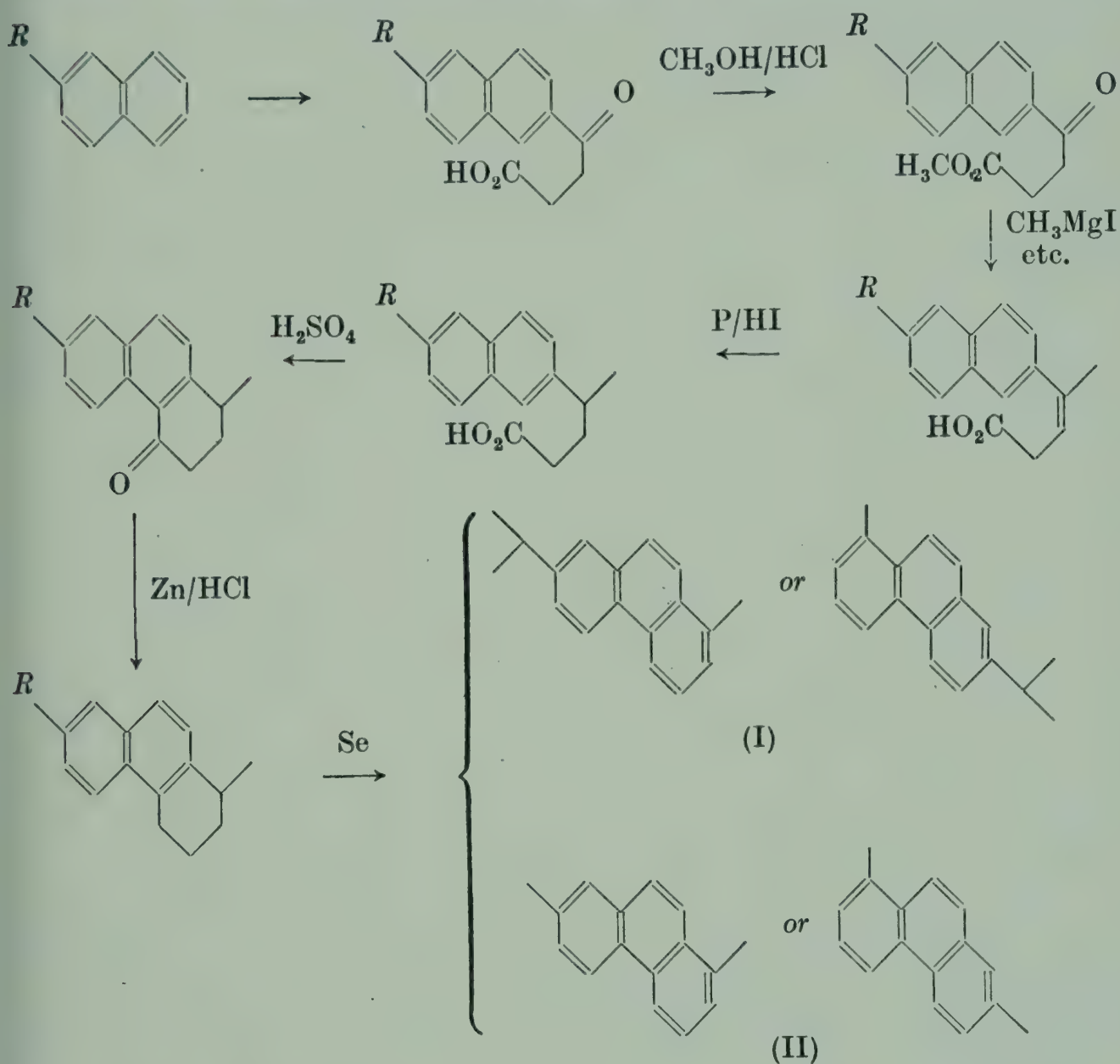
Although impure specimens of abietic acid and the pimaric acids were the subject of investigations more than a century ago, a full understanding of the chemistry of the diterpenoids has only been developed in the last twenty years. This period has seen remarkably rapid progress and, apart from certain minor points of stereochemistry, the structures of all the major diterpenoids have now been elucidated with certainty. For the most important and fundamental contributions to our present knowledge in this field we are undoubtedly indebted to the brilliant researches of Ruzicka and his school.

The importance of the method of dehydrogenation in establishing the nature of the carbon skeleton in sesquiterpene compounds has been already emphasised on p. 7. This method is of even greater importance in the study of diterpenoids and the whole chemistry of the group depends upon basic experiments involving dehydrogenation to aromatic compounds. The first application of the dehydrogenation method was made in the diterpenoid field by Vesterberg,* who obtained *retene* (I) from abietic acid by heating with sulphur. Retene was later isolated in a similar manner by the dehydrogenation of levopimaric acid.† A different derivative of phenanthrene called *pimanthrene*, 1:7-

* *Ber.* 1903, **36**, 4200.

† Ruzicka, Balas and Vilim, *Helv. Chim. Acta*, 1924, **7**, 458.

dimethylphenanthrene (II) was first obtained by Ruzicka and Balas* by the dehydrogenation of *d*-pimaric acid, and this hydrocarbon results also, usually together with other hydrocarbons, by the dehydrogenation of a number of other diterpenoids. The most numerous group of diterpenoids give, either



on direct dehydrogenation or on dehydrogenation of suitable derivatives, 1:7:8-*trimethylphenanthrene*, which was first obtained in this way by Ruzicka and Hosking† from a derivative of agathenedicarboxylic acid.

It is possible to make a classification of diterpenoids into bicyclic and tricyclic groups, but since the members of the bicyclic group, after suitable cyclisation, give the same dehydrogenation products as do the tricyclic group, it would seem preferable to adopt a system based purely on dehydrogenation

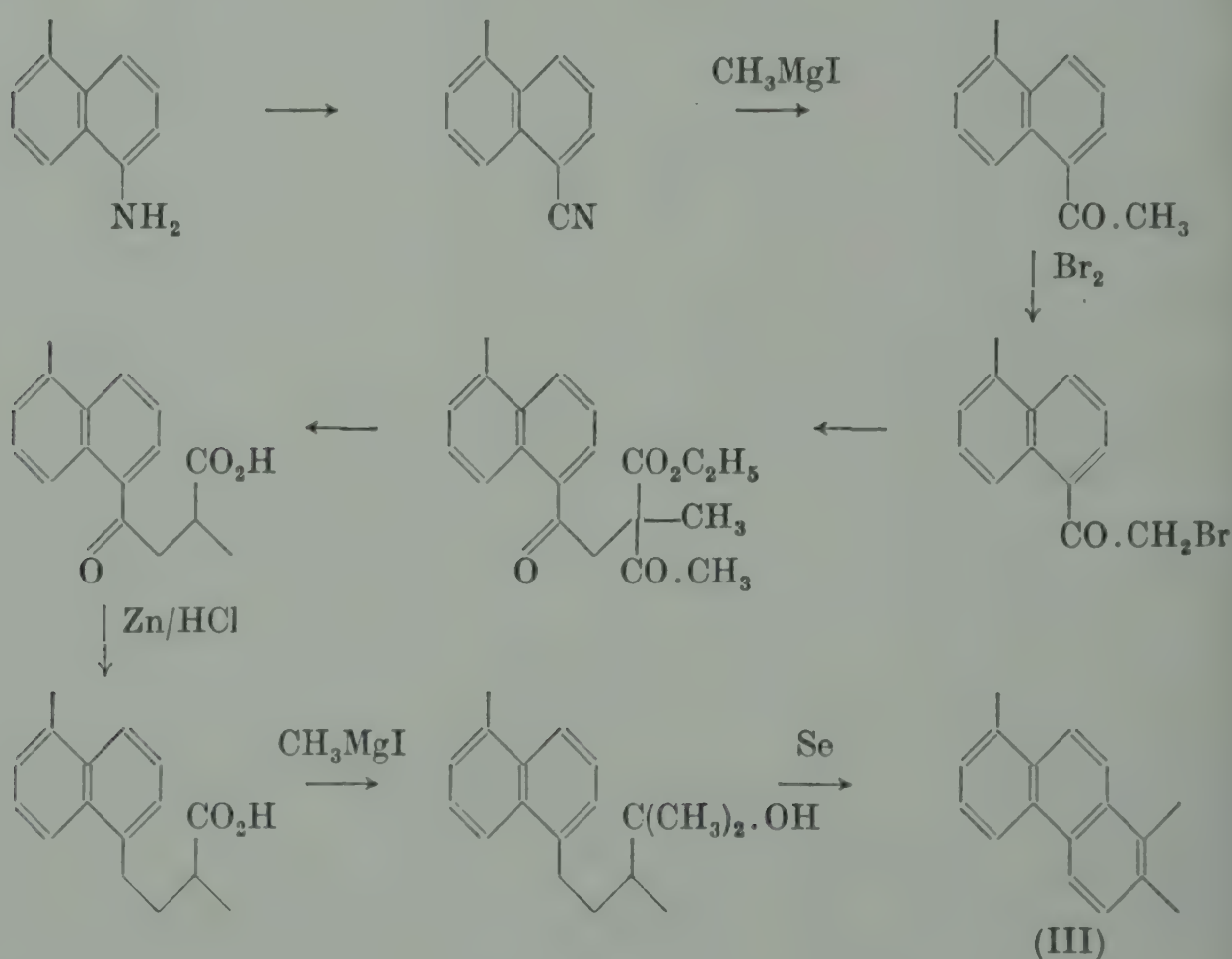
* *Helv. Chim. Acta*, 1923, 6, 677.

† *Ibid.* 1931, 14, 203.

experiments as has been done in the case of sesquiterpene compounds (see p. 4). One must distinguish therefore three main classes of diterpenoids, those giving retene, those giving pimanthrene and those giving 1:7:8-trimethylphenanthrene, recognising also that a number of diterpenoids give both pimanthrene and 1:7:8-trimethylphenanthrene.

The structures of retene and pimanthrene have been rigidly proved by their syntheses by Haworth, Letsky and Mavin* in accordance with the scheme on p. 329 ($R = -\text{CH}(\text{CH}_3)_2$ for retene and $R = -\text{CH}_3$ for pimanthrene). Syntheses of these hydrocarbons have also been effected by Bardhan and Sengupta† by somewhat different methods.

The synthesis of 1:7:8-trimethylphenanthrene has been described by Haworth and Mavin‡ in accordance with the scheme set out below:



The diterpenoids obey the Isoprene Rule as illustrated by the formulae for abietic acid (IV), *d*-pimaric acid (V), agathenedicarboxylic acid (VI), and for manoyl oxide (VII). The arrange-

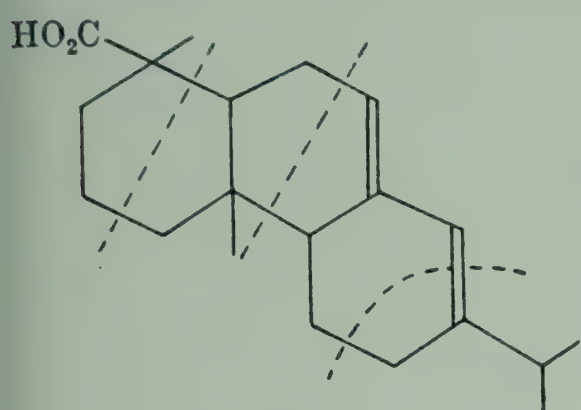
* *J.C.S.* 1932, p. 1784.

‡ *Ibid.* 1932, p. 2720.

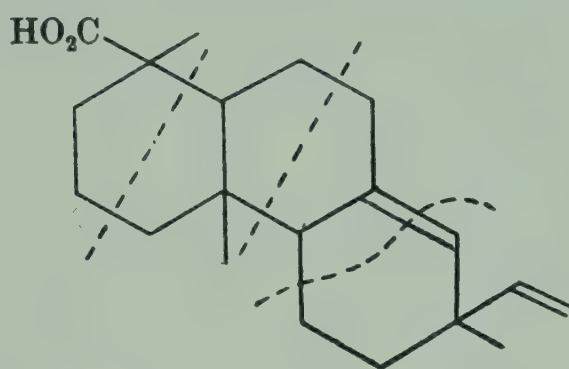
† *Ibid.* 1932, p. 2520.

ment of isoprene residues is not, however, always in regular order.

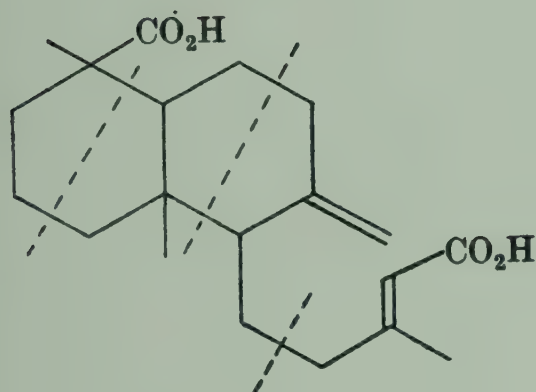
Some progress has already been made in our knowledge of the stereochemistry of the diterpenoids, and it is convenient to summarise here a tentative scheme covering the more important asymmetric centres in those compounds of established structure.



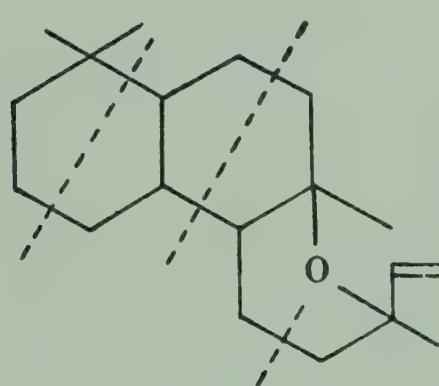
(IV)



(V)

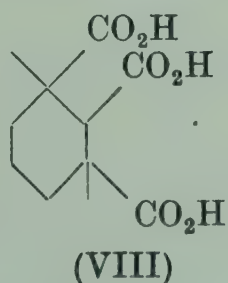


(VI)



(VII)

As is described in more detail on pp. 387, 451 vigorous oxidation of abietic acid (IV) and of *d*-pimaric acid (V) gives a $\text{C}_{11}\text{H}_{16}\text{O}_6$ tricarboxylic acid (VIII) derived from ring A. This acid is optically inactive, so that the 1 and 3 carboxyl groups must be in the *cis* relationship to each other. Since the carboxyl attached at position 2 has recently been shown by Barton and Schmeidler,* from a study of dissociation constant data to be related in the



(VIII)

* *J.C.S.* 1948, p. 1197; 1949, p. S 232.

trans sense to the other two carboxyl groups, the A/C ring fusion in abietic acid and related acids, must also be *trans*. The remaining asymmetric centre in abietic acid at C₁₃ is probably also in the *trans* relationship to the C₁₂ methyl group. This is so because it would be anticipated that treatment with acidic reagents (as in the preparation of abietic acid) would provide a mechanism for the assumption of the more stable configuration at this centre. There is support for this argument in the rearrangement of *isoabietic acid** to abietic acid under the influence of acidic reagents. From the strong laevorotation of abietic and levopimaric acids it is possible that they have the same configuration at C₁₃. *neo*Abietic acid, which is strongly dextrorotatory (p. 445) must by this reasoning have the opposite configuration to abietic acid at C₁₃.†

Although the carboxyl group in abietic acid is hindered sterically this hindrance is far more marked in podocarpic acid, which has the opposite configuration at C₁ (p. 475). The C₁ carboxyl in agathenedicarboxylic acid is similar in this respect to that in podocarpic acid. In addition agathenedicarboxylic acid affords on vigorous oxidation a C₁₁H₁₆O₆ tricarboxylic acid which is isomeric with that from abietic acid and which is optically active.‡ These experiments, although they show that the C₁ carboxyl of agathenedicarboxylic acid must be *cis* with respect to the C₁₂ methyl group, do not permit the elucidation of the configuration at C₁₁. However, this problem has recently been solved by Ruzicka, Zwicky and Jeger§ (see p. 471), who have interrelated agathenedicarboxylic acid and manool (see below) *via* a common derivative.

Since manool has been related directly to dehydroabietic acid (p. 353), it must have the same configurations as abietic acid at C₁₁ and C₁₂. This also establishes the configurations of manoyl oxide (p. 368), ketomanoyl oxide (p. 372) and sclareol (p. 360) at these centres, as well as that of agathenedicarboxylic acid (see above).

* The isomerism between the two acids is said to depend upon differing spatial arrangements at C₁₃; see p. 427.

† This argument was first advanced in Fieser and Fieser, *The Chemistry of Natural Products related to Phenanthrene*, New edition, 1949.

‡ Ruzicka and Bernold, *Helv. Chim. Acta*, 1941, **24**, 931.

§ *Helv. Chim. Acta*, 1948, **31**, 2143.

The conclusions on stereochemistry reached in this section are summarised in the table:

Diterpenoid	$C_1CO_2H:C_{11}H$	$C_{11}H:C_{12}CH_3$	$C_{12}CH_3:C_{13}H$
Abietic acid	<i>cis</i>	<i>trans</i>	<i>trans</i>
<i>iso</i> Abietic acid	<i>cis</i>	<i>trans</i>	<i>cis</i> ?
<i>neo</i> Abietic acid	<i>cis</i>	<i>trans</i>	<i>cis</i> ?
<i>d</i> -Pimaric acid	<i>cis</i>	<i>trans</i>	?
<i>levo</i> Pimaric acid	<i>cis</i>	<i>trans</i>	<i>trans</i>
Podocarpic acid	<i>trans</i>	<i>trans</i>	—
Agathenedicarboxylic acid	<i>trans</i>	<i>trans</i>	<i>trans</i>
Manool	—	<i>trans</i>	<i>trans</i>
Manoyl oxide	—	<i>trans</i>	<i>trans</i>
Ketomanoyl oxide	—	<i>trans</i>	<i>trans</i>
Sclareol	—	<i>trans</i>	<i>trans</i>
Ferruginol	—	<i>trans</i>	—

CHAPTER I

HYDROCARBONS

CAMPHORENE

The diterpene hydrocarbon *camphorene*,* $C_{20}H_{32}$, was found by Semmler and Rosenberg[†] to occur in the higher boiling hydrocarbon fraction of camphor oil. Later it was recognised by Semmler and Jonas[‡] to be identical with the *dimyrcene* prepared by Harries[§] by the action of heat on myrcene (see Vol. I, p. 16). It can also be prepared by heating linalool with anhydrous oxalic acid^{||} or by heating a mixture of myrcene and linalool.[¶] All these pyrolytic methods of preparation are effected using superatmospheric pressure, but camphorene has also been detected in small amount as a product of the thermal isomerisation of β -pinene under atmospheric pressure.**

Camphorene forms a characteristic *tetrahydrochloride*, m.p. 129–131°, from which pure camphorene, b.p. 177–178°/6 mm., d^{20}_D 0.8870, n_D 1.5034, $\alpha_D \pm 0^\circ$, can be regenerated by the action of basic reagents. It is monocyclic and has four double bonds as was deduced from the molecular refraction and from its catalytic hydrogenation to the saturated *octahydrocamphorene*, b.p. 174–176°/9 mm., d^{20}_D 0.8526, n_D 1.4647, $\alpha_D \pm 0^\circ$.^{††} From the method of its synthesis by the dimerisation of myrcene Ruzicka and Stoll^{‡‡} suggested that it probably had the carbon skeleton indicated in (I) and that it was formed as indicated in the scheme below, in an analogous manner to the polymerisation of isoprene to give dipentene (see Vol. I, p. xii). Although the formula (II) explains the reactions of camphorene it is unlikely to represent the hydrocarbon regenerated from the tetrahydrochloride (III),

* This hydrocarbon is usually termed α -camphorene, but since it is now proposed to call the isomeric β -camphorene simply *bicyclo-camphorene* it would seem preferable to drop the prefix. Compare Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, 7, 275, footnote 2.

[†] *Ber.* 1913, 46, 768.

[‡] *Ber.* 1913, 46, 1566; 1914, 47, 2068.

[§] *Ibid.* 1902, 35, 3264.

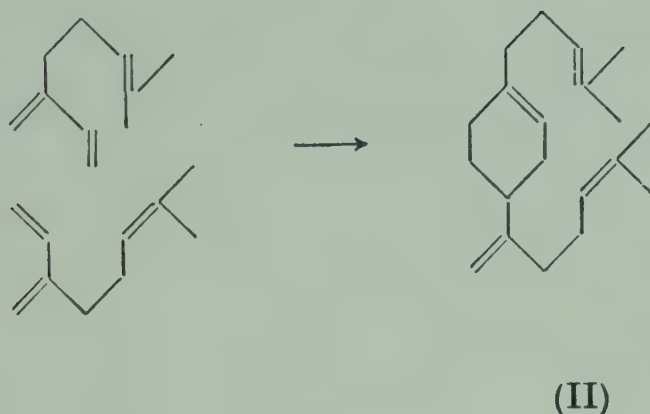
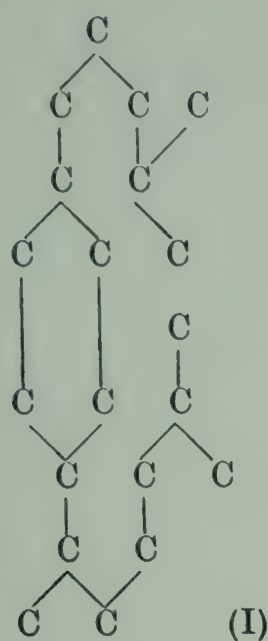
^{||} Semmler and Jonas, *ibid.* 1914, 47, 2068.

[¶] Kafuku, Oyamada and Nishi, *Bull. C.S. Japan*, 1933, 8, 144; *J.C.S. Japan*, 1933, 54, 364.

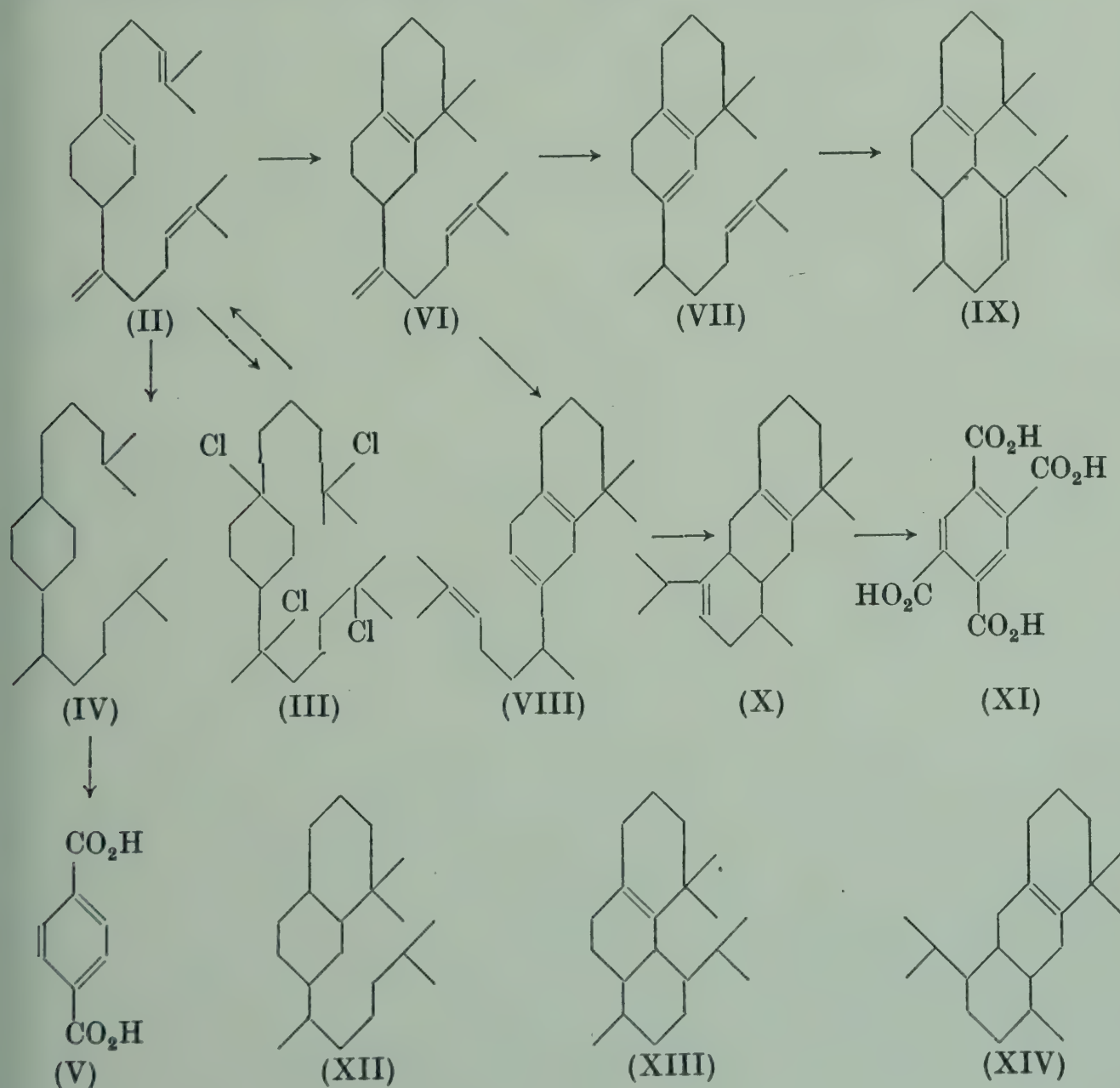
** Goldblatt and Palkin, *J. Amer. C.S.* 1941, 63, 3517; see Vol. II, p. 191.

^{††} Semmler and Rosenberg, *loc. cit.*

^{‡‡} *Helv. Chim. Acta*, 1924, 7, 271.



which is probably a mixture of isomers. Ruzicka and Stoll obtained support for the carbon skeleton (I) by the observation that octahydrocamphorene (IV) afforded *terephthalic acid* (V) on oxidation with manganese dioxide and sulphuric acid.



Camphorene is readily cyclised by acidic reagents, suitably formic acid, to *bicyclocamphorene*, b.p. 192–194°/12 mm., $d_4^{14^\circ}$ 0.9086, $n_D^{14^\circ}$ 1.5104, $\alpha_D \pm 0^\circ$, and to the doubly unsaturated *tricyclocamphorene*, b.p. 180–181°/12 mm., $d_4^{14^\circ}$ 0.9475, $n_D^{14^\circ}$ 1.5201, depending upon the experimental conditions employed.*

Bicyclocamphorene may be represented by either (VI), (VII), or (VIII), and it is doubtful if it is homogeneous.† *Tricyclocamphorene* would then be either (IX) or (X). Support is lent to the formulation (X) as correctly representing the tricyclic hydrocarbon by the observations of Ruzicka and Stoll, that on oxidation with manganese dioxide and sulphuric acid *pyromellitic acid* (XI) was obtained, which could not result in any simple manner from (IX). This finding does not, however, prove the absence of (IX) and it is still best to regard *tricyclocamphorene* as a mixture of both (IX) and (X).

By the catalytic hydrogenation of *bicyclocamphorene* Semmler and Jonas‡ prepared a *hexahydrobicyclocamphorene*, $C_{20}H_{38}$ (XII), b.p. 180–186°/14 mm., d^{21° 0.8588, n_D 1.4680, $\alpha_D \pm 0^\circ$, but, working doubtless under other conditions, Ruzicka and Stoll could only obtain from *tricyclocamphorene* a *dihydrotricyclocamphorene*, $C_{20}H_{34}$ (XIII) or (XIV), b.p. 176°/12 mm., $d_4^{14^\circ}$ 0.9410, $n_D^{14^\circ}$ 1.5118.

Camphorene can be characterised by the tetrahydrochloride mentioned above and also by the *tetrahydrobromide*, m.p. 133–134°.§

According to Kafuku, Oyamada and Nishi, a double bond isomer of camphorene, b.p. 176–178°/4.5 mm., $d_4^{19^\circ}$ 0.8875, $n_D^{19^\circ}$ 1.5030, *tetrahydrochloride*, m.p. 96–98°, *tetrahydrobromide*, m.p. 111–114°, is also formed during the pyrolytic synthesis from myrcene and linalool. Both camphorene and its isomer are said to give the same ill-defined *octabromide*, m.p. 70–80°.

* Ruzicka and Stoll, *loc. cit.*; compare Semmler and Jonas, *Ber.* 1914, **47**, 2068. The bicyclic so-called β -camphorene, which was suggested by Semmler and Rosenberg (*Ber.* 1913, **46**, 768) to be a constituent of camphor oil is doubtless an artefact formed from camphorene by isomerisation during the preparation of the tetrahydrochloride.

† There are a number of other possible positions for the double bonds which we have not considered it worth while to include.

‡ *Ber.* 1914, **47**, 2068.

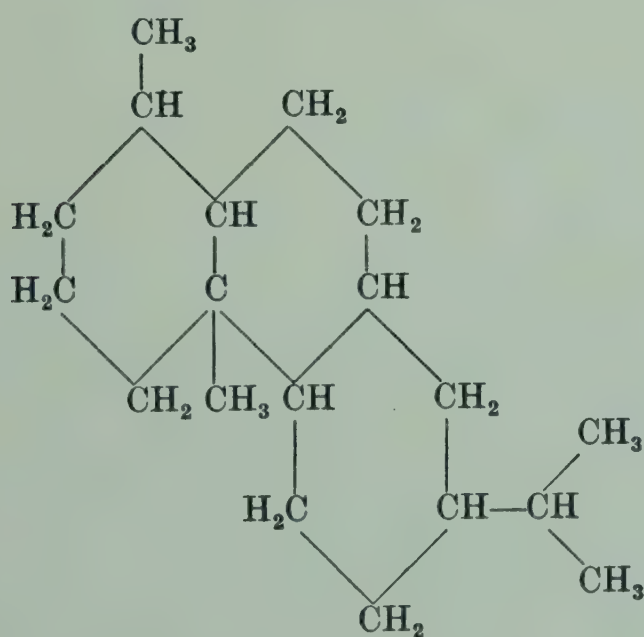
§ Kafuku, Oyamada and Nishi, *Bull. C.S. Japan*, 1933, **8**, 144; *J.C.S. Japan*, 1933, **54**, 364.

CRYPTOMERENE

Uchida* isolated from the leaf oil of *Cryptomeria japonica* Don. a diterpene hydrocarbon, $C_{20}H_{32}$, which he called α -cryptomerene. It was stated that this hydrocarbon, m.p. 61° , b.p. $198^\circ/15$ mm., $[\alpha]_D^{20} - 34.3^\circ$ (in chloroform), could be isomerised by treatment with hydrogen chloride in ethereal solution to a second hydrocarbon, β -cryptomerene, m.p. 211 – 212° . The melting-point of β -cryptomerene would seem to be anomalously high and its further investigation would appear to be desirable.

CUPRESSENE

The diterpene hydrocarbon *cupressene*, $C_{20}H_{32}$, m.p. 74 – 75° , $[\alpha]_D^{28} + 59.2^\circ$ (in $CHCl_3$), *hydrochloride*, m.p. 80 – 85° , was isolated by Briggs and Sutherland† from *Cupressus macrocarpa* Hartweg (syn. *C. Lambertiana* Carr.). Cupressene is tricyclic and contains two ethylenic linkages, for on catalytic hydrogenation it gave the saturated *tetrahydrocupressene*, m.p. 56 – 57.5° . Attempted dehydrogenation was unsuccessful and only *isophyllocladene* (p. 340) could be isolated from the reaction product. Whether the latter constituted an impurity in the starting material or not is uncertain.

FICHTELITE

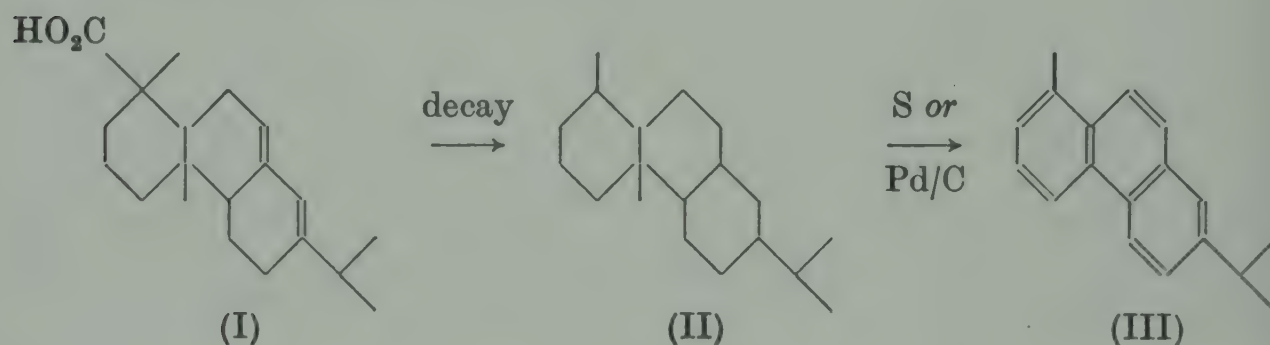
* *J. Amer. C.S.* 1916, 38, 687.

† *J. Org. Chem.* 1942, 7, 397.

Bromeis* isolated from the decayed wood of conifers a saturated hydrocarbon, $C_{19}H_{34}$, called *fichtelite*. It owes its formation to the decomposition under anaerobic conditions of the resin acids. This hydrocarbon, m.p. 46° , b.p. $235\text{--}236^\circ/43\text{ mm.}$, $d_4^{22^\circ} 0.9380$, $n_D^{20^\circ} 1.5052$, $d_4^{58^\circ} 0.9185$, $n_D^{58^\circ} 1.4942$, has been the subject of numerous investigations,[†] and Bamberger and Strasser[‡] suggested that it had the formula $C_{18}H_{32}$. Owing to its saturated character this early work threw little light on the structure of the hydrocarbon and it remained for Ruzicka, Balas and Schinz[§] to show that on dehydrogenation with sulphur it afforded *retene*. Subsequently Ruzicka and Waldmann^{||} found by quantitative dehydrogenation with palladised charcoal that it really had the formula $C_{19}H_{34}$ and this was confirmed by X-ray analysis.[¶]

In view of the relationship of *fichtelite* to abietic acid (I) and *retene* (III), Ruzicka and Waldmann have suggested that the hydrocarbon is most probably represented by (II).

Sterling and Bogert** have synthesised a hydrocarbon of the structure (II), which was a mixture of stereoisomers, one of which was probably *fichtelite*.



The partial dehydrogenation of *fichtelite* has been studied recently by Perold and Jeger.^{††}

* *Annalen*, 1841, **37**, 304; compare Trommsdorff, *ibid.* 1837, **21**, 126.

† Clark, *Annalen*, 1857, **103**, 236; Mallet, *Ber.* 1872, **5**, 817; *Chem. News*, 1872, **26**, 159; Bamberger, *Ber.* 1889, **22**, 635; Hell, *ibid.* 1889, **22**, 498; Liebermann and Spiegel, *ibid.* 1889, **22**, 780; Spiegel, *ibid.* 1889, **22**, 3369; compare also Walden, *Chem. Ztg.* 1900, **30**, 393.

‡ *Ber.* 1889, **22**, 3361.

§ *Helv. Chim. Acta*, 1923, **6**, 692.

|| *Ibid.* 1935, **18**, 611.

¶ Crowfoot, *J.C.S.* 1938, p. 1241.

** *Science*, 1938, **87**, 196; *J. Org. Chem.* 1939, **4**, 20.

†† *Helv. Chim. Acta*, 1949, **32**, 1085.

KAURENE

The tetracyclic diterpene, *kaurene*, $C_{20}H_{32}$, m.p. $59-60^{\circ}$, $d_4^{106^{\circ}}$ 0.9282, $n_D^{100^{\circ}}$ 1.4912, was first isolated by Hosking* from the leaf oil of the kauri pine (*Agathis australis*), endemic to New Zealand. The presence of one double bond was shown by catalytic hydrogenation to the saturated hydrocarbon *dihydrokaurene*, $C_{20}H_{34}$, m.p. $86-87^{\circ}$, $[\alpha]_D^{21^{\circ}} - 32^{\circ}$ (in chloroform[†]), and by the formation of a *monohydrochloride*, m.p. $110-111^{\circ}$. Recently Briggs and Cawley[‡] have reinvestigated the essential oil of *Agathis australis*, using rather more mild conditions than those employed by Hosking. They obtained thereby not kaurene, but α -podocarpene (see p. 342), and it has been concluded that the former hydrocarbon is impure.[§]

Dihydrokaurene has been shown to be identical with dihydro- α -podocarpene.

MIRENE

The name *mirene* was originally given to a hydrocarbon isolated by Hosking and Short^{||} from the leaf oil of *Podocarpus ferruginea* (the miro pine), a tree growing in New Zealand. Its nature was investigated further by Hosking.[¶] However, more recent work by Briggs, Cawley, Loe and Taylor** has demonstrated the inhomogeneity of Hosking's original hydrocarbon, which has been shown to be a mixture of phyllocladene, *d*- α -podocarpene and a new hydrocarbon, $C_{20}H_{32}$, m.p. $59-60^{\circ}$, $[\alpha]_D^{20^{\circ}} + 43.8^{\circ}$ (in chloroform). The name *mirene* should now be used for this substance only.

On catalytic hydrogenation mirene afforded *dihydromirene*, m.p. $63-64^{\circ}$. Since this derivative was saturated, mirene must be tetracyclic. This was confirmed by isomerisation by heating with glacial acetic acid to give *isophyllocladene* (see below), and by the formation of a saturated *monohydrochloride*, $C_{20}H_{33}Cl$, m.p. 82° , $[\alpha]_D^{15^{\circ}} + 59.9^{\circ}$ (in chloroform).

* *Rec. trav. Chim.* 1928, **47**, 578.

† Briggs and Taylor, *J.C.S.* 1950, p. 407.

‡ *J.C.S.* 1948, p. 1888.

§ Briggs and Taylor, *loc. cit.*

|| *Rec. trav. chim.*, 1928, **47**, 834.

¶ *Ibid.* 1930, **49**, 1036.

** *J.C.S.* 1950, p. 955.

PHYLLOCLADENE

The tetracyclic diterpene, *phyllocladene*, $C_{20}H_{32}$, m.p. 98° , $[\alpha]_D^{25} + 15.8^\circ$ (in chloroform) has been found to be fairly widely distributed in nature. It was first isolated by Baker and Smith* in 1910 from the leaf oil of *Phyllocladus rhomboidalis* and was later described under the names *dacrene*, from *Dacrydium biforme* and *Dacrydium Colensoi*,† and *sciadopitene*, from *Sciadopitys verticillata*.‡ *Phyllocladene* has also been obtained from the leaf oils of *Phyllocladus alpinus*, *Araucaria excelsa* and *Dacrydium cupressinum*,§ and of *Podocarpus spicata* grown in the North Island of New Zealand.|| *Phyllocladene* and *isophyllocladene* occur together in the essential oil of *Phyllocladus trichomanoides*.¶

Phyllocladene has only one ethylenic linkage as is shown by the formation of a *monohydrochloride*, m.p. 106° , $[\alpha]_D^{20} + 7.77^\circ$ (in benzene), a *monohydrobromide*, m.p. $141\text{--}142^\circ$ decomp., $[\alpha]_D^{17} + 8.06^\circ$ (in chloroform), a *dibromide*, m.p. $122\text{--}123^\circ$, $[\alpha]_D^{18} + 9.34^\circ$ (in chloroform), and by its catalytic hydrogenation, when a mixture of α -*dihydrophyllocladene*, m.p. $74\text{--}74.5^\circ$, $[\alpha]_D^{16} + 23.9^\circ$ (in chloroform) and β -*dihydrophyllocladene*, m.p. $55\text{--}56^\circ$, $[\alpha]_D^{16} + 12.5^\circ$ (in chloroform) is obtained, both hydrocarbons being saturated. The carbon skeleton of *phyllocladene* has been partially identified by dehydrogenation with selenium, when a mixture of pimanthrene (I) and retene (II) is obtained,** together with two ill-defined hydrocarbons of unknown constitution. The isomeric hydrocarbon, *isophyllocladene*, m.p. $110.5\text{--}112^\circ$, $[\alpha]_D^{17} + 23.4^\circ$ (in chloroform), is formed when *phyllocladene* hydrochloride is treated with aniline or potassium acetate, or when *phyllocladene* itself is digested with alcoholic sulphuric acid. *isoPhyllocladene* forms a monohydrochloride and a monohydrobromide identical with those of *phyllocladene*, but the

* *Pines of Australia*, p. 4190.

† Goudie, *J.S.C.I.* 1923, **42**, 357 T; Aitken, *ibid.* 1928, **47**, 223 T; Blackie, *ibid.* 1929, **48**, 357 T; 1930, **49**, 26 T.

‡ Nishida and Uota, *J. Agric. C.S. Japan*, 1935, **11**, 489; *idem*, *ibid.* 1936, **12**, 308; Uota, *J. Dept. Agric. Kyushu Imp. Univ. Japan*, 1937, **5**, 117; compare Nishida and Uota, *J. Agric. C.S. Japan*, 1930, **6**, 1078; 1931, **7**, 157, 957.

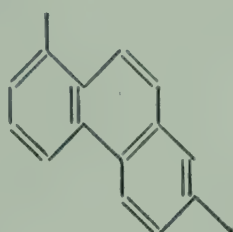
§ Briggs, *J.C.S.* 1937, p. 79; compare Brandt, *New Zealand J. Sci. Tech.* 1938, **20**, 8 B.

|| Briggs and Loe, *J.C.S.* 1950, p. 958.

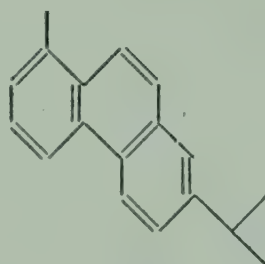
¶ Briggs and Sutherland, *J. Org. Chem.* 1948, **13**, 4.

** Brandt *loc. cit.*; compare Uota, *loc. cit.*

dibromide, m.p. 133–134° decomp., is different. On catalytic hydrogenation, *isophyllocladene* gave the saturated α -dihydro-*phyllocladene* mentioned above. The simple relationship existing between *phyllocladene* and *isophyllocladene* indicated by these observations has been confirmed by oxidation experiments.*



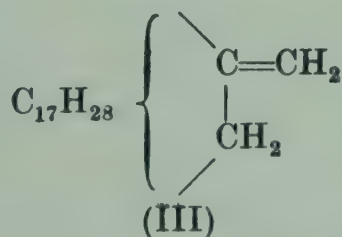
(I)



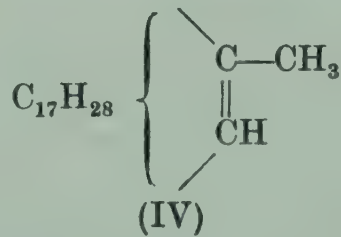
(II)

On potassium permanganate oxidation *phyllocladene* gave a *glycol*, $C_{20}H_{34}O_2$, m.p. 172–173°, *diacetate*, m.p. 134° and a *ketone*, $C_{19}H_{30}O$, m.p. 100–101°, *semicarbazone*, m.p. ca. 230–231° decomp., whilst under more drastic conditions a *dicarboxylic acid*, $C_{19}H_{30}O_4$, m.p. 200–203° decomp., was obtained. On mild oxidation with potassium permanganate *isophyllocladene* afforded a *ketonic acid*, $C_{20}H_{32}O_3$, m.p. 166–167°, *semicarbazone*, m.p. ca. 296° decomp., degraded further by sodium hypobromite to the same *dicarboxylic acid*, m.p. 200–203° decomp., as was obtained from *phyllocladene*. This acid also resulted from the more drastic oxidation with potassium permanganate of *isophyllocladene*.

These experiments show that *phyllocladene* and *isophyllocladene* must be related in the same way as the β - and α -pinenes (Vol. II, pp. 105, 191), as indicated in the partial formulae (III) for *phyllocladene* and (IV) for *isophyllocladene*. This has been conclusively proved by the ozonolysis of the two hydrocarbons, when *phyllocladene* furnished formaldehyde and the ketone, $C_{19}H_{30}O$, mentioned above, and *isophyllocladene* gave the same ketonic acid, m.p. 166–167°, as was obtained on potassium permanganate oxidation. On the basis of all these experiments and from the reported relationship between *isophyllocladene* and



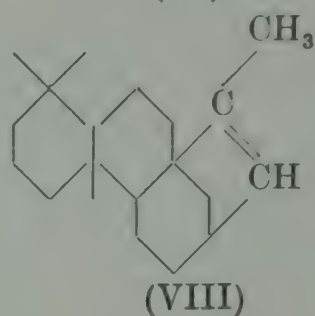
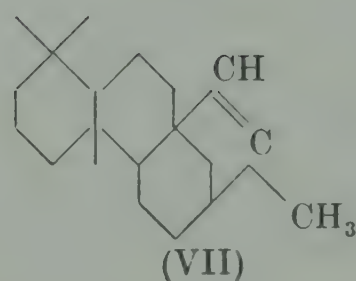
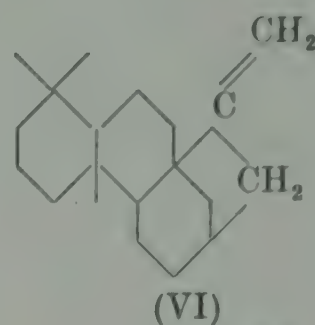
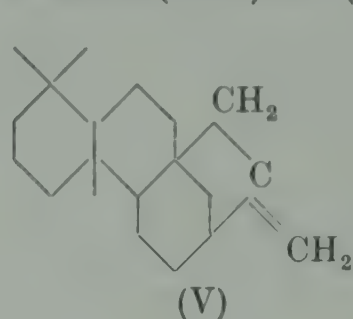
(III)



(IV)

* Nishida and Uota, *loc. cit.*; Uota, *loc. cit.*

rimuene (see p. 344), Brandt has suggested the formulae (V) or (VI) as representations of phyllocladene, when *isophyllocladene* will be either (VII) or (VIII).



Phyllocladene can be characterised by the formation of a *nitrosochloride*, m.p. 128°, a *nitrosite*, m.p. 132–133° decomp., and a *nitrosate*, m.p. 129.5°, as well as by the preparation of many of the other derivatives to which reference has already been made. Both phyllocladene and *isophyllocladene* are reported to give the same saturated tricyclic hydrocarbon, C₂₀H₃₆, b.p. 175–176°/6 mm., $[\alpha]_D + 10.59^\circ$ (in chloroform), on reduction with red phosphorus and hydriodic acid at 150–250°.

Briggs* has shown that the α -dihydrophyllocladene mentioned above is identical with *iosene* and various other hydrocarbons which have been obtained from lignites.†

PODOCARPRENE

Nishida and Uota‡ isolated from the essential oil of *Podocarpus macrophylla* Don. a diterpene hydrocarbon, α -podocarprene, C₂₀H₃₂, m.p. 50°, $[\alpha]_D^{11} - 71.9^\circ$ (in chloroform). The same hydrocarbon was obtained shortly afterwards by Kawamura from the essential oil of *Sciadopitys verticillata*. α -Podocarprene gave a *hydrochloride*, m.p. 115–117°, a *nitrosochloride*, decomp. 136°, a *nitrosate*, decomp. 140°, a *nitrolpiperidide*, m.p. 167°, and

* J.C.S. 1937, p. 1035.

† Compare Ciusa and Galazzi, *Gazz.* 1921, 51, I, 55; Ciusa and Croce, *ibid.* 1922, 52, I, 125; Soltys, *Monatsh.* 1929, 53–54, 175.

‡ J. Agric. C.S. Japan, 1931, 7, 157.

afforded on catalytic hydrogenation the saturated *dihydro- α -podocarprene*, $C_{20}H_{34}$, m.p. 86–87°, $[\alpha]_D^{90} - 29.3^\circ$ (in chloroform). It must therefore be tetracyclic. More recently Briggs and Cawley* have reinvestigated the essential oil of *Agathis australis* from which Hosking† had previously isolated *kaurene* (see p. 339). When the oil was worked up under rather more mild conditions than those employed by Hosking, the diterpenoid hydrocarbon isolated was found to be identical with α -podocarprene.

Besides α -podocarprene Nishida and Uota‡ obtained a second isomeric diterpene from the essential oil of *Podocarpus macrophylla* Don. which they called β -podocarprene. Since this hydrocarbon was an oil, b.p. 173–177°/3 mm., $n_D^{20} 1.5203$, $[\alpha]_D^{20} - 15.9^\circ$, it may not have been homogeneous. It gave the same hydrochloride as did α -podocarprene. When this hydrochloride was heated with alcoholic caustic potash it furnished α -podocarprene together with a further isomer, γ -podocarprene, m.p. 197–199°. β -Podocarprene, on catalytic hydrogenation, was reduced to *dihydro- β -podocarprene*, b.p. 203–204°/17 mm., $n_D 1.5121$, $[\alpha]_D^{20} + 7.8^\circ$.

Kawamura§ investigated the action of alcoholic potassium acetate on the hydrochloride of α -podocarprene and found that a further diterpene, δ -podocarprene, m.p. 65°, $[\alpha]_D^{11} - 27.1^\circ$ (in chloroform), was formed thereby. δ -Podocarprene gave a *nitrosate*, decomp. 126° and a *dinitrosate*, decomp. 157°. On catalytic hydrogenation it furnished *dihydro- α -podocarprene* and with hydrogen chloride α -podocarprene hydrochloride was reformed. δ -Podocarprene differs, therefore, from α -podocarprene in the same way that *isophyllocladene* differs from *phyllocladene* (see p. 341), and the name *isopodocarprene* would be a convenient alternative.

On heating with glacial acetic acid or with alcoholic sulphuric acid α -podocarprene gave the δ -isomer. *d- α -Podocarprene*, m.p. 49°, $[\alpha]_D + 101^\circ$ (in chloroform), has been obtained recently from the essential oil of *Podocarpus ferruginea*.||

* J.C.S. 1948, p. 1888.

† Rec. trav. chim. 1928, 47, 578; 1930, 49, 1036.

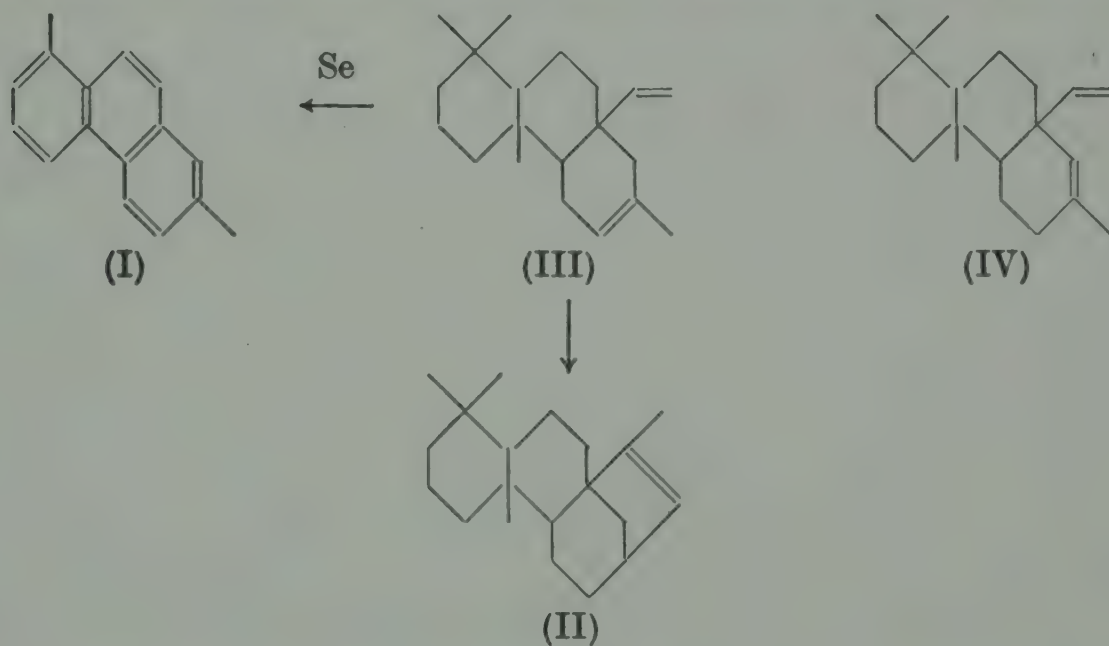
‡ Loc. cit.

§ Loc. cit.

|| Briggs, Cawley, Loe and Taylor, J.C.S. 1950, p. 955.

RIMUENE

The tricyclic diterpene, *rimuene*, $C_{20}H_{32}$, m.p. 55° , $[\alpha]_D + 44.7^\circ$ (in chloroform), was first isolated by McDowall and Finlay* from the essential oil of the rimu tree (*Dacrydium cupressinum*), endemic to New Zealand. It is apparently identical with the diterpene, *totarene*, isolated by Beath,† from the essential oil of the totara tree (*Podocarpus Totara*). On catalytic hydrogenation *rimuene* is stated to absorb hydrogen in two successive stages to give firstly *dihydrorimuene*, $C_{20}H_{34}$, m.p. 77° , and then the saturated hydrocarbon, *tetrahydrorimuene*, $C_{20}H_{36}$, m.p. 26° .‡ On ozonolysis *rimuene* afforded formaldehyde and unidentified products, thus indicating the presence of a methylene group, and by dehydrogenation with selenium *pimanthrene* (I) was obtained.§ On digestion with formic acid *rimuene* was isomerised to the tetracyclic hydrocarbon, *isophyllocladene*, possibly (II) (see p. 342), and from this fact, and the experimental results described above, Brandt has suggested the provisional formula (III), but the alternative (IV), which is an analogue of an earlier formula for *d*-pimaric acid (see p. 454), would seem equally possible.



Rimuene can be characterised by the formation of a *mono-hydrochloride*, m.p. 63° , a *nitrosochloride*, m.p. $86-88^\circ$ decomp., and a *tetrabromide*, m.p. $55-60^\circ$.

* *J.S.C.I.* 1925, **44**, 42 T.

† *Ibid.* 1933, **52**, 338 T; compare Aitken, *ibid.* 1929, **48**, 344 T.

‡ Carrie, *ibid.* 1932, **51**, 367 T.

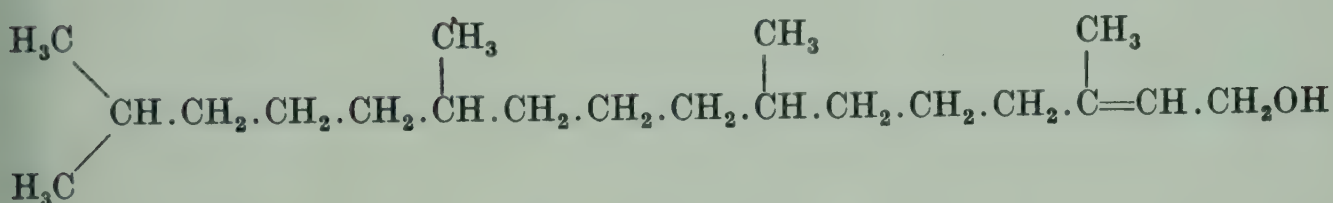
§ Brandt, *New Zealand J. Sci. Tech.* 1938, **20**, 8.

CHAPTER II

ALCOHOLS AND PHENOLS

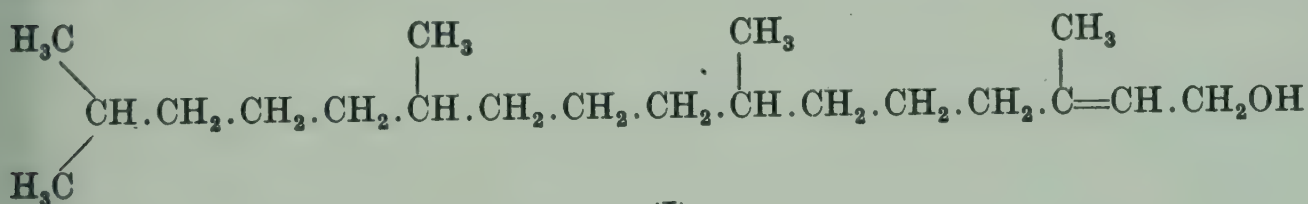
A. ACYCLIC ALCOHOL

PHYTOL

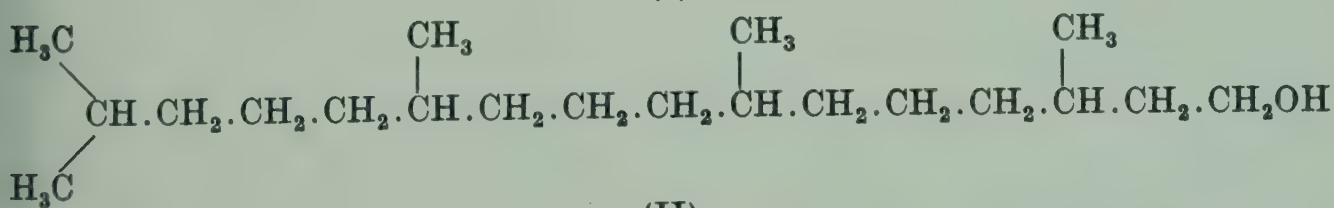


The diterpenoid alcohol, *phytol*, $\text{C}_{20}\text{H}_{40}\text{O}$, was discovered by Willstätter* to be the alcoholic moiety of the chlorophyll molecule. It is possibly present also in the non-saponifiable fraction of cod liver oil.† In more recent years the phytol chain has been recognised to comprise part of the molecules of the Vitamins E and of Vitamin K_1 .

Phytol (I), b.p. $145^\circ/0.03\text{--}0.04\text{ mm.}$, $203\text{--}204^\circ/9\text{--}10\text{ mm.}$, $d_4^{20^\circ} 0.852$, $n_D^{20^\circ} 1.4638$,‡ was characterised as a mono-unsaturated primary alcohol by its ease of esterification and the ease of hydrolysis of its esters, and by its catalytic or electrolytic reduction to the saturated primary alcohol, *dihydrophytol*, $\text{C}_{20}\text{H}_{42}\text{O}$



(I)



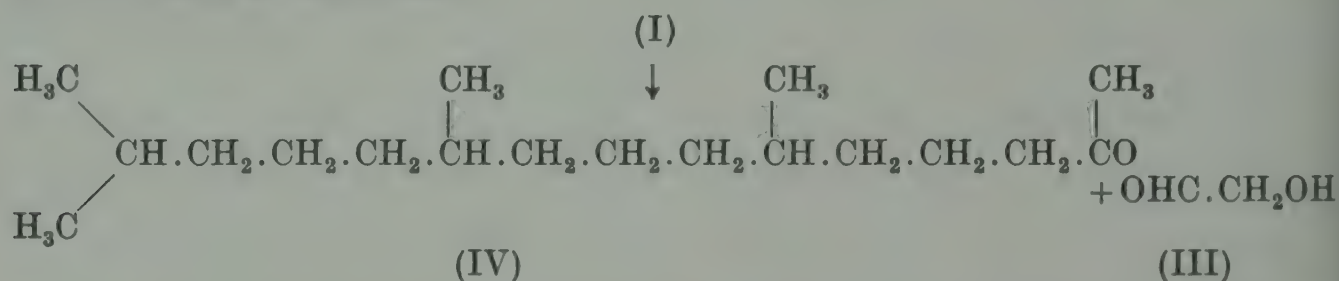
(II)

* Willstätter and Hocheder, *Annalen*, 1907, **354**, 205; Willstätter, Hocheder and Hug, *ibid.* 1909, **371**, 1; Willstätter and Oppé, *ibid.* 1911, **378**, 1; for a more recent description of the preparation of phytol from this source see Fischer and Oestreicher, *Zeit. Physiol. Chem.* 1940, **262**, 243.

† Drummond, Channon and Coward, *Biochem. J.* 1925, **19**, 1047.

‡ The ultra-violet absorption spectrum of phytol has been studied by Bednarczyk and Marchlewski (*Bull. intern. acad. polon. sci. Classe. sci. math. nat.* 1937, **A**, p. 187), and its infra-red spectrum by Stair and Coblenz (*J. Res. Nat. Bur. Stand.* 1933, **11**, 703).

(II), b.p. 201.5–202°/9.5 mm., d_4^{20} 0.8398, n_D^{20} 1.4521,* *allophanate*, m.p. 73°.† The initial degradational experiments of Willstätter‡ did not lead to a successful elucidation of the structure of phytol, and this was only effected at a later date by the synthetic experiments of Fischer.§ Fischer found that phytol, on ozonolysis, afforded a saturated *ketone*, $C_{18}H_{36}O$, b.p. 173.5–174°/10 mm., d_4^{25} 0.8323, n_D^{25} 1.4432 (*semicarbazone*, m.p. 66–67°; *potassium salt* of 1-naphthylhydrazone-4-sulphonic acid, m.p. 163–165° decomp.), and *glycollic aldehyde* (III), thus showing the double bond to be in the $\alpha:\beta$ -position to the alcoholic grouping. The ketone, $C_{18}H_{36}O$, could also be obtained by the oxidation of phytol with chromic acid and had actually been prepared in an impure state in the earlier experiments of Willstätter. Fischer, from a consideration of the application of the isoprene rule, suggested that the ketone might be 2: 6: 10: *trimethyl-14-pentadecanone* (IV), and proved this by its synthesis from hexahydrofarnesyl bromide.|| Fischer finally proved that phytol must have the structure (I), by the conversion of this ketone (IV), to a synthetic phytol identical with that prepared from natural sources.¶



Natural phytol usually has a negligibly small optical rotatory power and this has been taken to imply that it is a racemate.** However, Karrer *et al.*†† have recently described the isolation of an optically active phytol, $[\alpha]_D^{18} + 0.20\text{--}0.21^\circ$, from nettles and

* Willstätter and Hocheder, *loc. cit.*; Willstätter and Mayer, *Ber.* 1908, **41**, 1475; Willstätter, Mayer and Huni, *Annalen*, 1911, **378**, 73; compare Kuhn and Suginomé, *Helv. Chim. Acta*, 1929, **12**, 916.

† Karrer and Bretscher, *Helv. Chim. Acta*, 1943, **26**, 1758.

‡ Willstätter, Mayer and Huni, *loc. cit.*; Willstätter, Schuppli and Mayer, *Annalen*, 1918, **418**, 121.

§ *Annalen*, 1928, **464**, 69; Fischer and Lowenberg, *ibid.* 1929, **475**, 183.

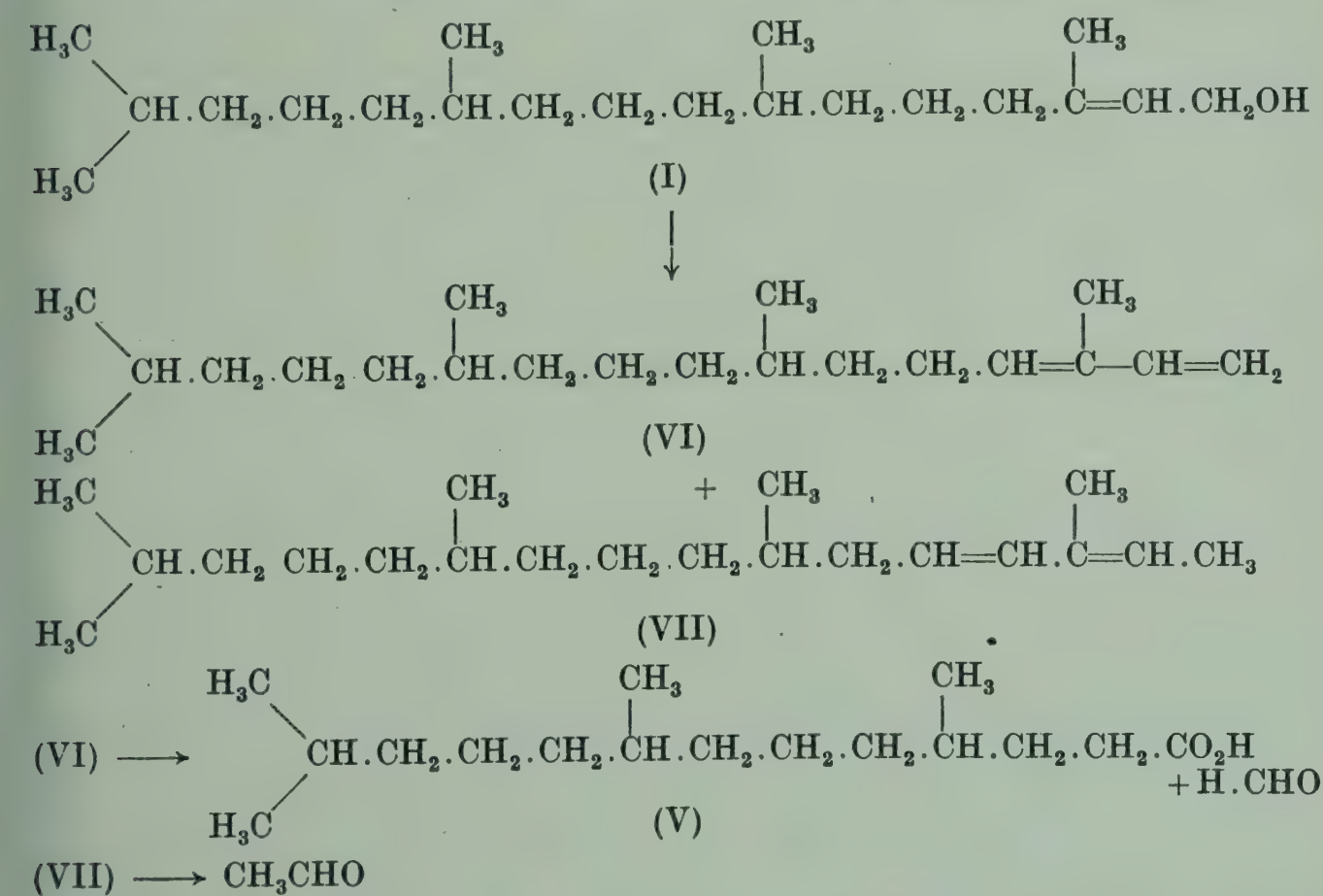
|| See p. 120; for later syntheses see Smith and Spring, *J. Amer. C.S.* 1943, **65**, 1276; Karrer *et al.*, *Helv. Chim. Acta*, 1943, **26**, 1741.

¶ Compare Karrer *et al.*, *loc. cit.*

** See Fischer and Lowenberg, *loc. cit.*; Wagner-Jauregg, *Zeit. physiol. Chem.* 1933, **222**, 21.

†† *Helv. Chim. Acta*, 1943, **26**, 1741.

from *d*-citronellol have synthesised a laevorotatory phytol, $\alpha_D - 0.18^\circ$, which must be asymmetric at C_6 and racemic at C_{10} . This synthetic phytol and the dextrorotatory phytol are not, as might have been thought, optical antipodes, as has been shown by Karrer, Simon and Zbinden* in the following way. When phytol is treated with dehydrating agents, for example by boiling a benzene solution of phytol and phthalic anhydride or, better, with anhydrous oxalic acid, a doubly unsaturated hydrocarbon, *phytadiene*, $C_{20}H_{38}$, b.p. *ca.* $186-187^\circ/13$ mm., d_4^{20} 0.826 , is obtained.† Karrer, Kugler and Simon‡ found that phytadiene on ozonolysis afforded *formaldehyde*, 4: 8: 12-*trimethyltridecanoic acid* (V), and some *acetaldehyde*, thus showing that the hydrocarbon must consist principally of (VI) admixed with some (VII), in agreement with its ultra-violet absorption spectrum, which has λ_{\max} $232\text{ m}\mu$ with $\log \epsilon = 4.22$ (in hexane). Whilst the



d-phytadiene from the naturally occurring *d*-phytol had $\alpha_D + 0.89^\circ$, the corresponding *l*-phytadiene obtained from the synthetic alcohol had only $\alpha_D - 0.25^\circ$. The two hydrocarbons cannot therefore be optical antipodes. Karrer, Simon and Zbinden

* *Helv. Chim. Acta*, 1944, 27, 313.

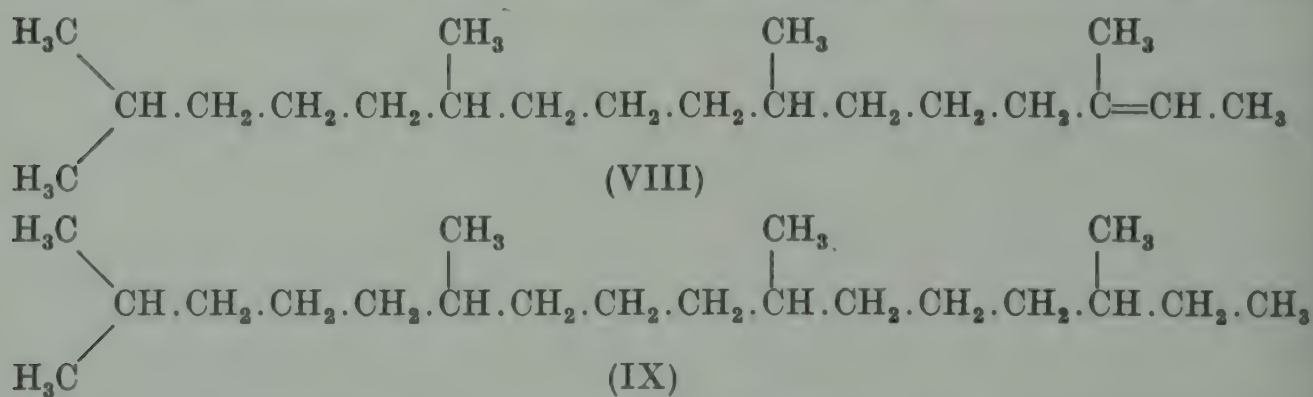
† Willstätter, Mayer and Huni, *Annalen*, 1911, 378, 73.

‡ *Helv. Chim. Acta*, 1944, 27, 1006.

conclude that natural phytol is *not* a racemate but a latently optically active compound. If this is so then it would seem reasonable to suppose that the configurations at C₆ and C₁₀ are either + - or - + in natural phytol, which would account for its low rotatory power.

Phytol can be characterised by the formation of the *silver salt* of the *hydrogen phthalate*, m.p. 117–119°, the *semicarbazone* of the *pyruvic acid ester*, m.p. 72–75°, the *phenylurethane*, m.p. 26–29°, the *α-naphthylurethane*, m.p. 24–30°, and specially by the *allophanate*, m.p. 71°, and the *hydrogen 3-nitrophthalate*, m.p. 99.5–100°.*

Phytol forms an *iodide* on treatment with hydriodic acid in acetic acid solution from which, by action of zinc dust, the unsaturated hydrocarbon *phytene*, C₂₀H₄₀ (VIII), b.p. 167–168°/7.5 mm., d_4^{20} 0.817, can be prepared.† On catalytic hydrogenation phytene affords the saturated hydrocarbon, *phytane*, C₂₀H₄₂ (IX), b.p. 169.5°/9.5 mm., d_4^{20} 0.803, which has also been obtained as a by-product in the reduction of phytol to dihydrophytol (see above).‡ The synthesis of the α:β-unsaturated acid,



phytenoic acid (X), b.p. 174°/0.4 mm., d_4^{20} 0.893, corresponding to phytol has been described by Karrer, Epprecht and König.‡ The same acid is obtained as a by-product in the oxidation of phytol with chromic acid.¶ On catalytic hydrogenation it furnished *phytanoic acid* (XI), b.p. 165–172°/0.2 mm., d_4^{20} 0.8761,

* Willstätter and Hocheder, *Annalen*, 1907, **354**, 205; Fischer and Lowenberg, *ibid.* 1929, **475**, 183; Karrer *et al.*, *Helv. Chim. Acta*, 1943, **26**, 1741; Lennartz, *Ber.* 1943, **76**, 248.

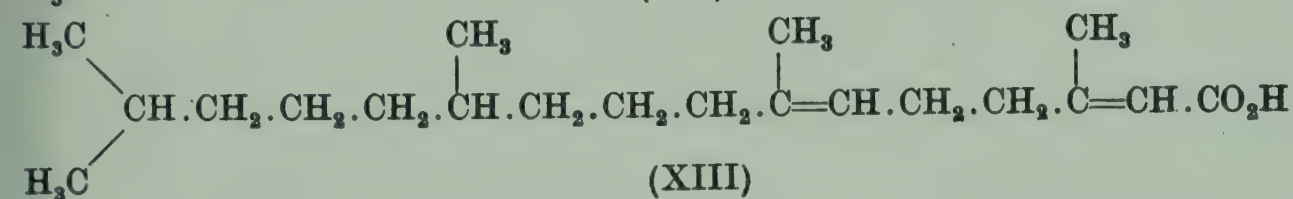
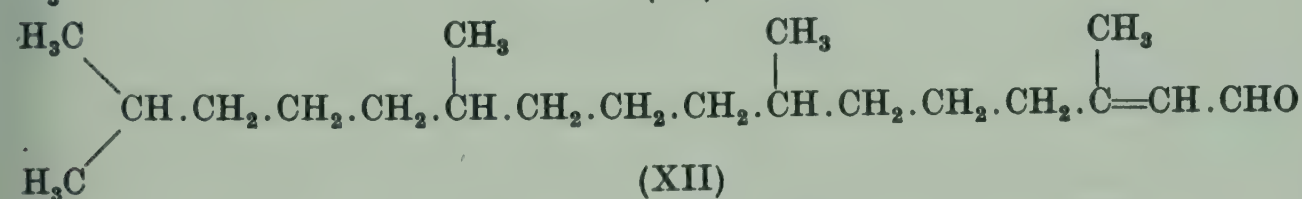
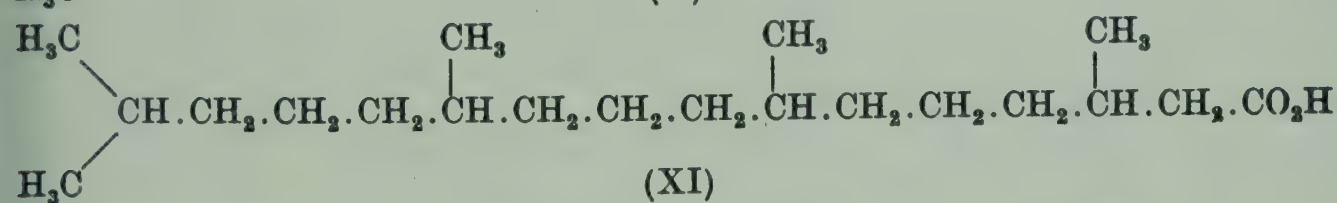
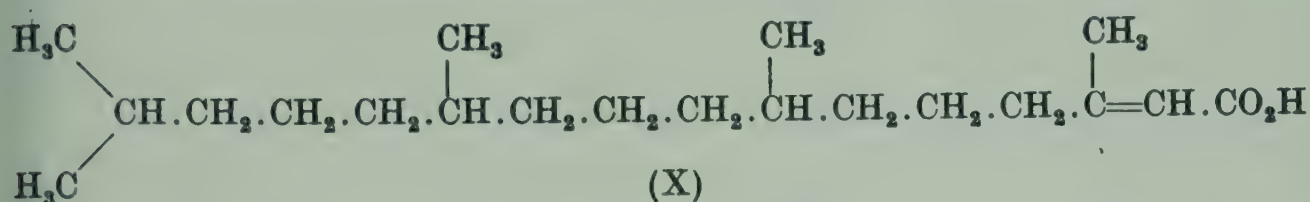
† Willstätter and Hocheder, *Annalen*, 1907, **354**, 205; Willstätter, Mayer and Huni, *ibid.* 1911, **378**, 73.

‡ Willstätter and Mayer, *Ber.* 1908, **41**, 1475; Willstätter, Mayer and Huni, *loc. cit.*

§ *Helv. Chim. Acta*, 1940, **23**, 272.

¶ Willstätter, Mayer and Huni, *Annalen*, 1911, **378**, 73; Fischer, *ibid.* 1928, **464**, 69.

acid chloride, b.p. 166–170°/0.5 mm., amide, m.p. 53–53.5°, which can also be prepared by the oxidation of dihydrophytol.* The synthesis of the aldehyde, *phytenal* (XII), b.p. 157°/0.3 mm., has been effected by Karrer and Epprecht,[†] and the synthesis of the related $\Delta^{2,6}$ -*phytadienoic acid* (XIII), b.p. 164°/0.25 mm., $d_{14}^{14^\circ}$ 0.9024, has been described by Karrer and König.[‡]



The behaviour of phytol in the animal body has been studied by Fischer and Bielig.[§] Surface films of phytol and phytanoic acid have been examined by Ställberg and Stenhagen.^{||}

Dihydrophytol forms a *bromide*, b.p. 161°/0.8 mm., $d_4^{20^\circ}$ 0.9738, $n_D^{20^\circ}$ 1.4651, and an *iodide*, b.p. 152–154°/0.12–0.22 mm., $d_4^{20^\circ}$ 1.0791, $n_D^{20^\circ}$ 1.4799.[¶]

* Compare Willstätter, Mayer and Huni, *loc. cit.*; Karrer, Epprecht and König, *loc. cit.*

† *Helv. Chim. Acta*, 1941, **24**, 1039.

‡ *Ibid.* 1941, **24**, 304.

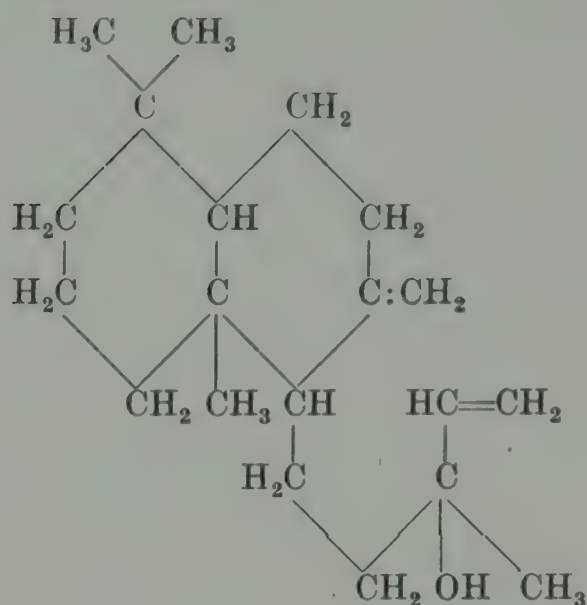
§ *Zeit. Physiol. Chem.* 1940, **266**, 73.

|| *Svensk. Kem. Tid.* 1941, **53**, 44.

¶ Kuhn and Suginomé, *Helv. Chim. Acta*, 1929, **12**, 916.

B. DICYCLIC ALCOHOL

MANOOL



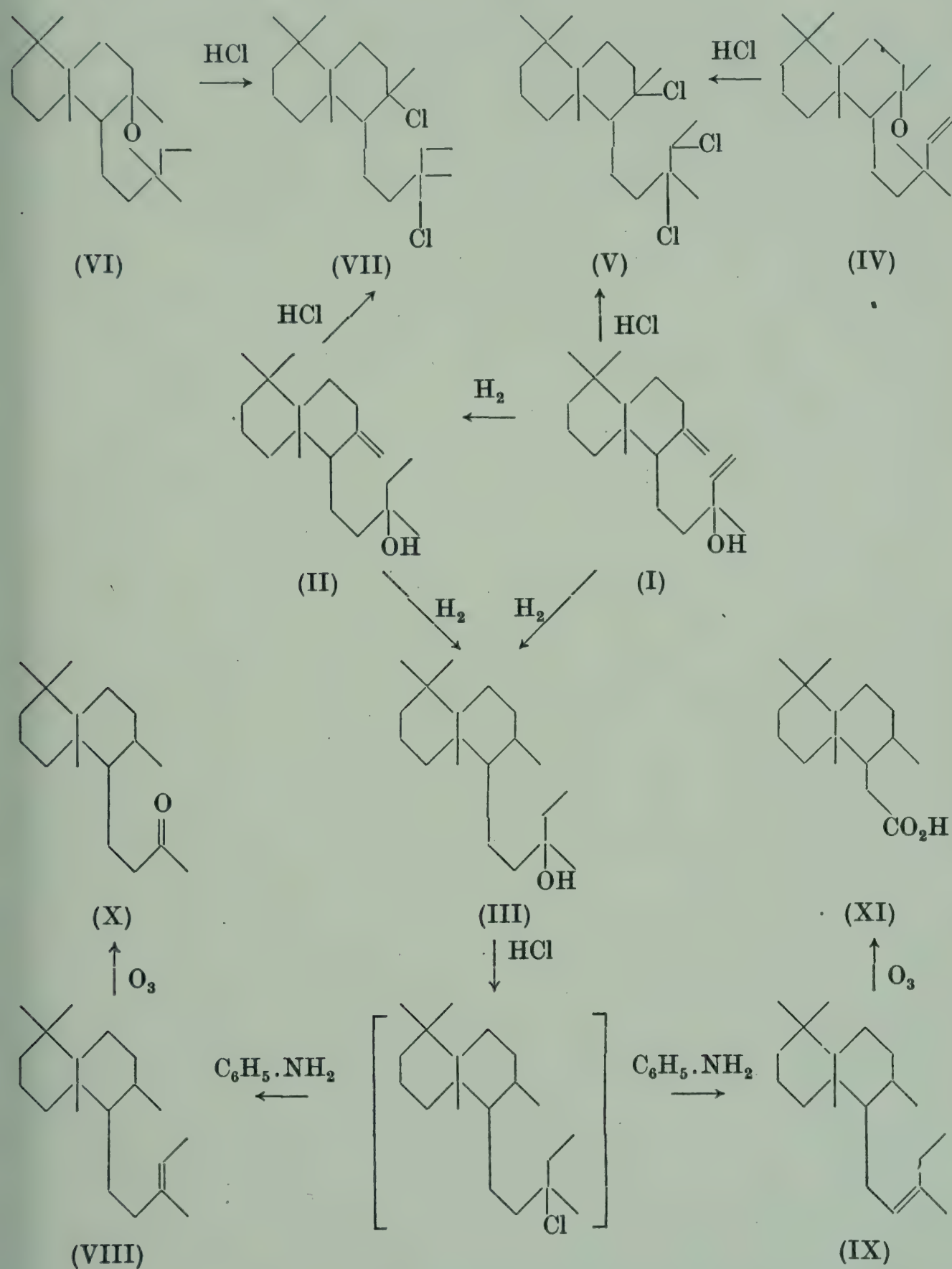
The diterpene alcohol, *manool*, $C_{20}H_{34}O$ (I), m.p. 53° , b.p. $144\text{--}145^\circ/0.2\text{ mm.}$, $d_4^{19^\circ} 0.9712$, $n_D^{19^\circ} 1.5156$, $[\alpha]_D^{19^\circ} +30.4^\circ$ (in alcohol), was isolated by Hosking and Brandt* from the wood oil of the yellow pine (*Dacrydium biforme*).

Manool contains two ethylenic linkages, since it can be catalytically hydrogenated in two stages to give *dihydromanool*, $C_{20}H_{36}O$ (II), m.p. $44\text{--}45^\circ$, b.p. $151\text{--}152^\circ/0.2\text{ mm.}$, $d_4^{16^\circ} 0.9361$, $n_D^{16^\circ} 1.4931$ and *tetrahydromanool*, $C_{20}H_{38}O$ (III), m.p. $55\text{--}56^\circ$. It must be closely related in structure to manoyl oxide (IV) (see p.368), since on treatment with hydrogen chloride it yields the same *trihydrochloride* (V), m.p. 119° , as is obtained by the action of this reagent on the oxide, whilst from dihydromanool and dihydromanoyl oxide (VI) the same dihydrochloride (VII), m.p. $121\text{--}122^\circ$, can be prepared. These results suggested that manool was the tertiary alcohol represented by (I).

By the action of hydrogen chloride on tetrahydromanool a hydrochloride was formed yielding on digestion with aniline a hydrocarbon, *tetrahydromanoene*, $C_{20}H_{26}$, b.p. $141\text{--}142^\circ/0.2\text{ mm.}$, $d_4^{20^\circ} 0.9158$, $n_D^{20^\circ} 1.5030$. This hydrocarbon was not homogeneous and was most probably a mixture of (VIII) and (IX) since it gave on ozonolysis a ketone, $C_{18}H_{32}O$ (X), *semicarbazone*, m.p. 202° , and an *acid*, $C_{16}H_{28}O_2$ (XI), m.p. 129° , $[\alpha]_D +10.8^\circ$ (in

* *Ber.* 1935, **68**, 1311; *New Zealand J. Sci. Tech.* 1936, **17**, 755.

chloroform), *anilide*, m.p. 153–154°. The formation of these two degradation products provides conclusive proof that the hydroxyl



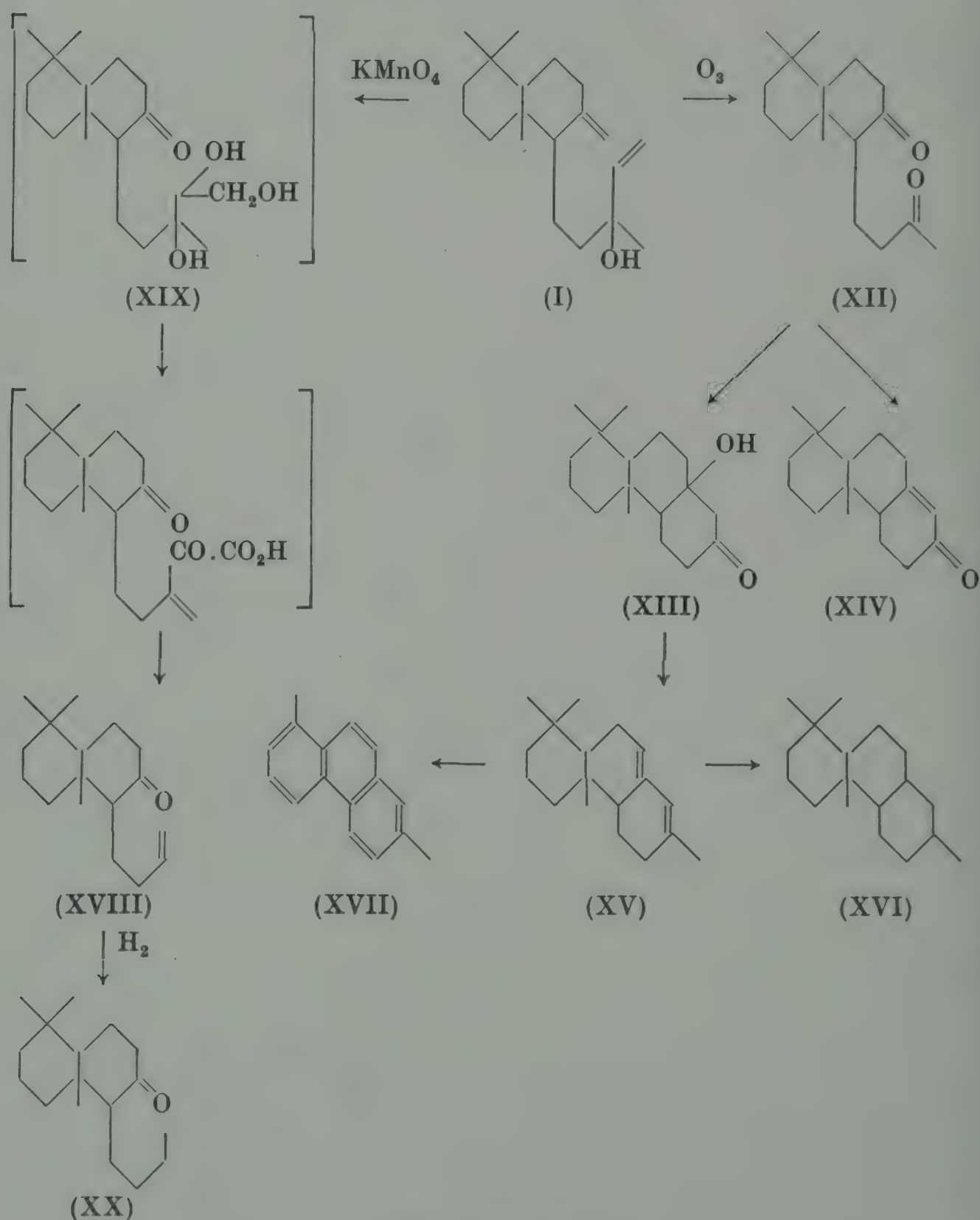
group in manool must be as shown in formula (I). The acid (XI) has also been obtained by Ruzicka, Dürst and Jeger* from the triterpenoid, ambrein. This is the first occasion on which a direct

* *Helv. Chim. Acta*, 1947, **30**, 358.

relationship has been established between a triterpenoid and a diterpenoid.

Whilst the positions of the two ethylenic linkages in manool can be deduced from the relationship of the alcohol to manoyl oxide, direct proof was obtained by its oxidation with ozone and potassium permanganate.

Hosking* showed that on ozonolysis manool gave a *diketone*, $C_{17}H_{28}O_2$ (XII), b.p. 159–160°/0.1 mm., $d_4^{22^\circ}$ 1.042, $n_D^{22^\circ}$ 1.5095,



* Ber. 1936, 69, 780.

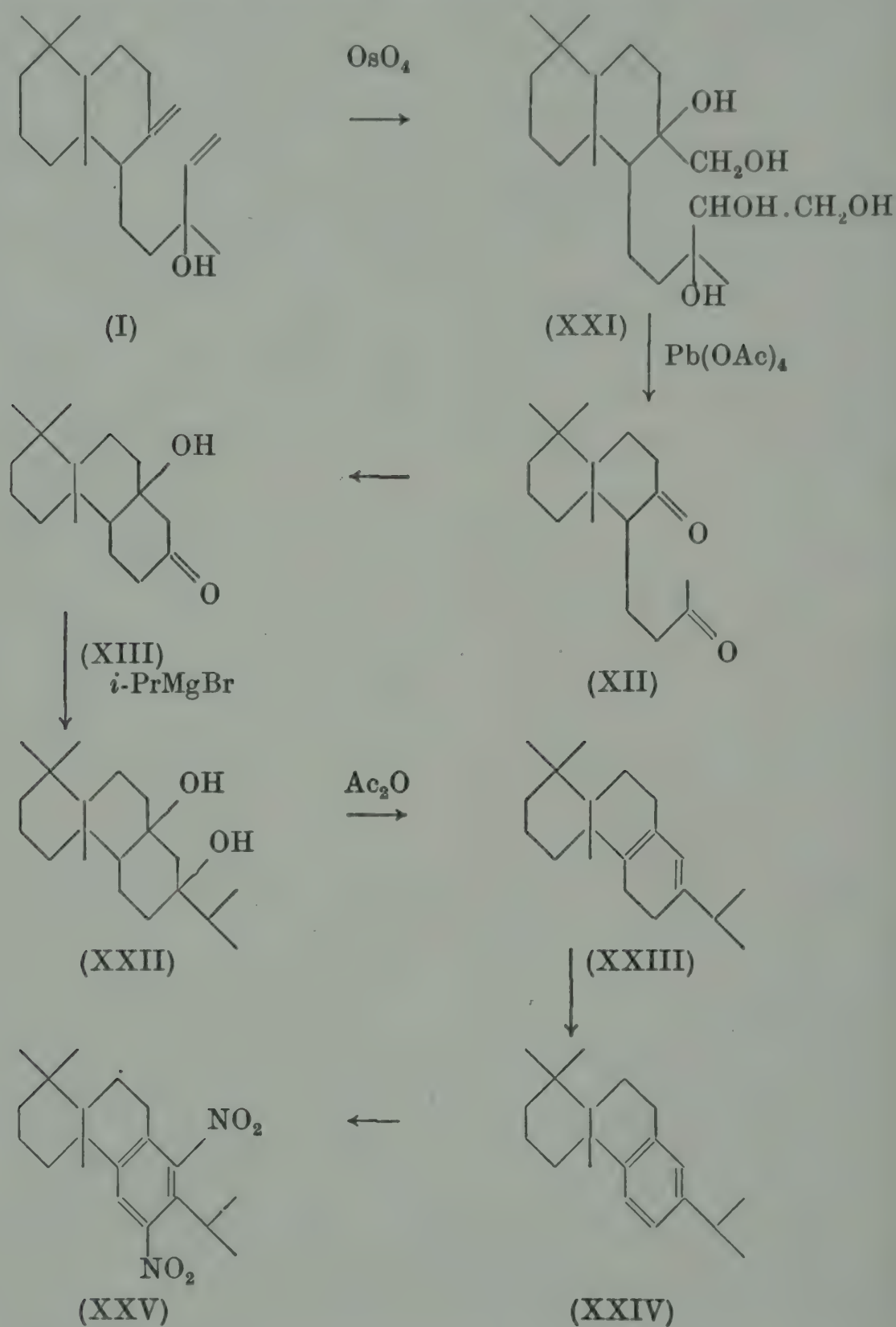
in which the carbonyl groups were in the 1:5-position, since it gave with alkali the *hydroxy-ketone* (XIII), m.p. 199°, or the unsaturated *ketone*, $C_{17}H_{26}O$ (XIV), m.p. 71°, $d_4^{18^\circ}$ 1.045, $n_D^{18^\circ}$ 1.5400, *semicarbazone*, m.p. 212–213°, depending upon the reaction conditions. A study of the action of magnesium methyl iodide on the hydroxy-ketone followed by distillation provided further evidence in support of the structure (XIII) assigned to it. This reaction resulted in the formation of a tricyclic *hydrocarbon*, $C_{18}H_{28}$ (XV), b.p. 127–130°/0.1 mm., containing two ethylenic linkages, which on catalytic hydrogenation gave the saturated *hydrocarbon*, $C_{18}H_{32}$ (XVI), b.p. 120°/0.1 mm. By selenium dehydrogenation of this former hydrocarbon *pimanthrene* (XVII) was obtained.

On oxidation with potassium permanganate manool gave an unsaturated *ketone*, $C_{17}H_{28}O$, b.p. 137–138°/0.1 mm., $d_4^{19^\circ}$ 0.9840, $n_D^{19^\circ}$ 1.5903, *semicarbazone*, m.p. 185–186°. This ketone has been formulated as (XVIII), being formed probably from the primary oxidation product (XIX) as indicated in the formulae. By catalytic hydrogenation a saturated *ketone*, $C_{17}H_{30}O$ (XX), $d_4^{19^\circ}$ 0.9800, $n_D^{19^\circ}$ 1.5026, *semicarbazone*, m.p. 199–200°, was prepared.

Recently Jeger, Dürst and Büchi* have established a direct relationship between manool and abietic acid. Manool, treated with osmium tetroxide, afforded a pentahydric *alcohol*, $C_{20}H_{38}O_5$ (XXI), m.p. 184–185°, $[\alpha]_D + 5^\circ$ (in alcohol), which, on oxidation with lead tetra-acetate, gave a *hydroxy-ketone*, m.p. 202–203°, $[\alpha]_D + 36^\circ$ (in chloroform), identical with (XIII). By treatment with isopropyl magnesium bromide (XIII) afforded the dihydric *alcohol* (XXII), dehydrated by acetic anhydride to the diene (XXIII), which, in turn, was dehydrogenated by N-bromosuccinimide to the *hydrocarbon* (XXIV). This hydrocarbon, although not obtained crystalline, must have been identical with dehydroabietane (p. 425), for it gave 6:8-dinitrodehydroabietane, $C_{20}H_{28}O_4N_2$ (XXV), m.p. 187–188°, $[\alpha]_D + 56^\circ$ (in chloroform) on nitration, identical in all respects with an authentic specimen prepared *via* dehydroabietinal from dehydroabietic acid. These experiments provide not only complete confirmation of the formula of manool but also prove that the fusion of

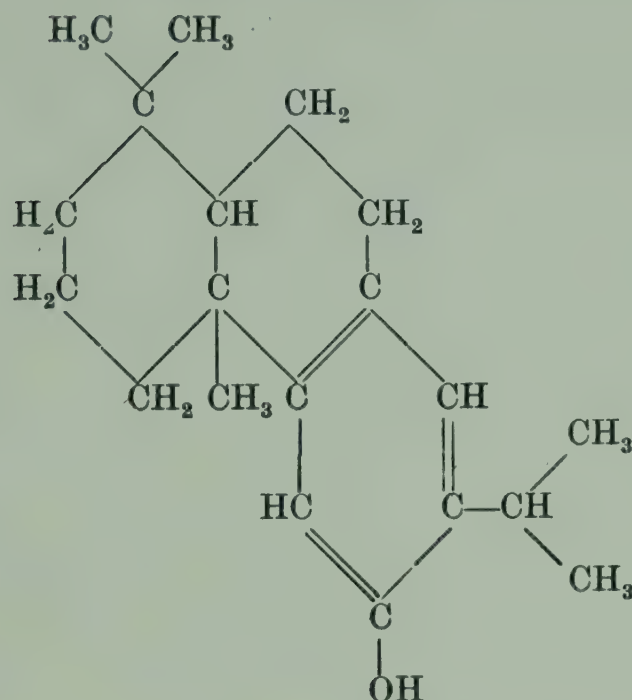
* *Helv. Chim. Acta*, 1947, 30, 1853.

rings A and B in the manool group of diterpenoids must be *trans* as in abietic acid and related resin acids (see p. 333).



Manool can be most conveniently characterised by the preparation of the trihydrochloride referred to above. It is dehydrated by digestion with formic acid, yielding a tricyclic hydrocarbon, $\text{C}_{20}\text{H}_{32}$, b.p. $121^\circ/0.3$ mm., $d_4^{18^\circ}$ 0.9482, $n_D^{18^\circ}$ 1.5179.

C. TRICYCLIC PHENOLS

FERRUGINOL

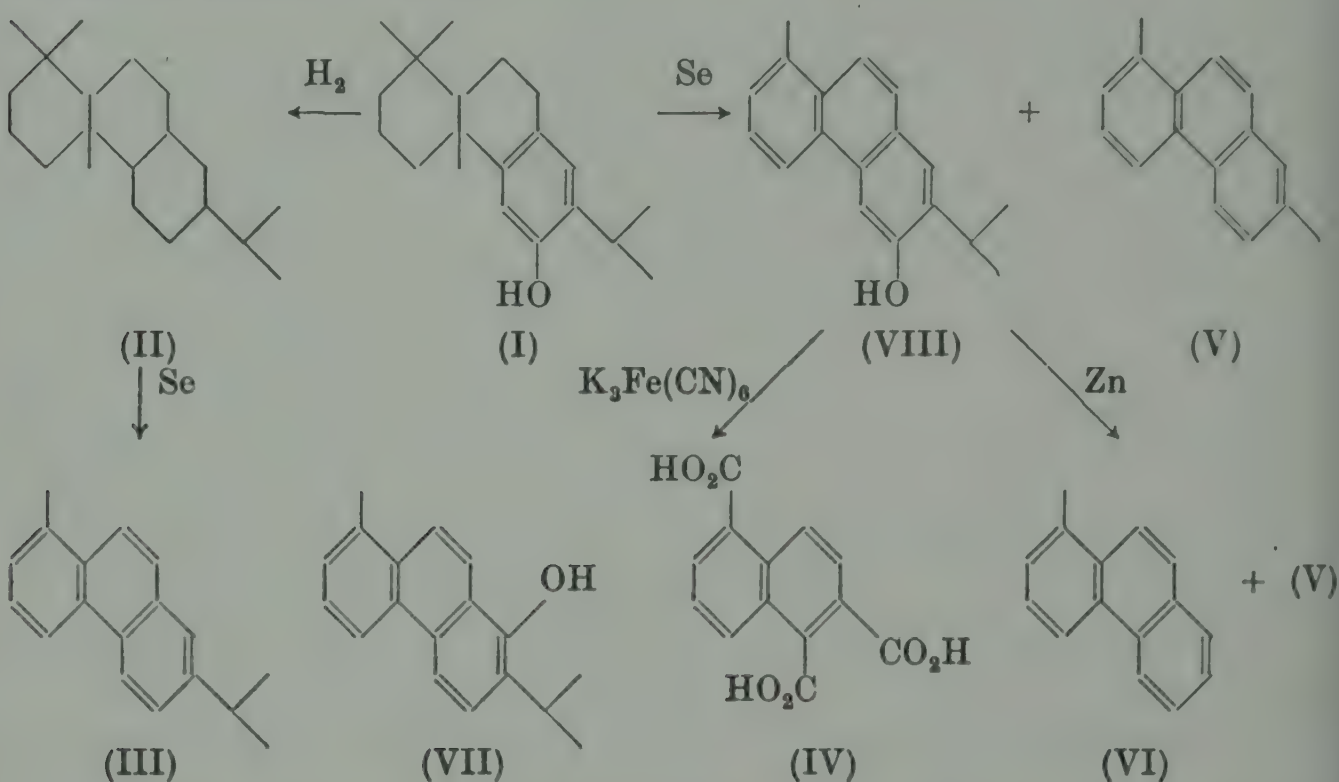
The phenolic diterpenoid resinol, *ferruginol*, $C_{20}H_{30}O$ (I), b.p. $175^{\circ}/0.3$ mm., $[\alpha]_D^{16^{\circ}} + 40.6^{\circ}$ (in alcohol), comprises the major part of the resin of the miro tree (*Podocarpus ferruginea*), endemic to New Zealand.*

The chemistry of ferruginol has been examined in some detail by Brandt and Neubauer.[†] The presence of a phenolic grouping was proved by the appreciable solubility of ferruginol in sodium hydroxide solution, by its absorption spectrum, by perbenzoic acid titration, and by the fact that ferruginol did not form a hydrogen phthalate. This view is in agreement with the green coloration given by ferruginol in the presence of ferric chloride solution, and with the red dye formed by coupling with diazotised sulphanilic acid in alkaline solution. On catalytic hydrogenation both ferruginol and its acetate (see below) gave a saturated hydrocarbon, *ferruginane*, $C_{20}H_{36}$ (II), b.p. $139-140^{\circ}/0.3$ mm., $[\alpha]_D^{18^{\circ}} + 37.4^{\circ}$ (in alcohol), which was converted by dehydrogenation with selenium into *retene* (III). On treatment with the latter reagent ferruginol, itself, furnished a *phenol*, $C_{18}H_{18}O$, m.p. 178° , *picrate*, m.p. $176-177^{\circ}$, *styphnate*, m.p. 172° , *acetate*, m.p. $90-91^{\circ}$,

* Brandt and Neubauer, *J.C.S.* 1939, p. 1031; compare Easterfield, *Trans. New Zealand Inst.* 1910, **43**, 53.

[†] *Loc. cit.*

which was oxidised by potassium ferricyanide to *naphthalene-1:5:6-tricarboxylic acid* (IV), and some pimanthrene (V). Pimanthrene, together with 1-methylphenanthrene (VI), was also obtained by zinc dust distillation of the phenol. Brandt and Neubauer were of the opinion that this phenol was 8-*hydroxyretene* (VII), but it was shown subsequently by Campbell and Todd* that this was incorrect, and that the phenol was actually 6-*hydroxyretene* (VIII).

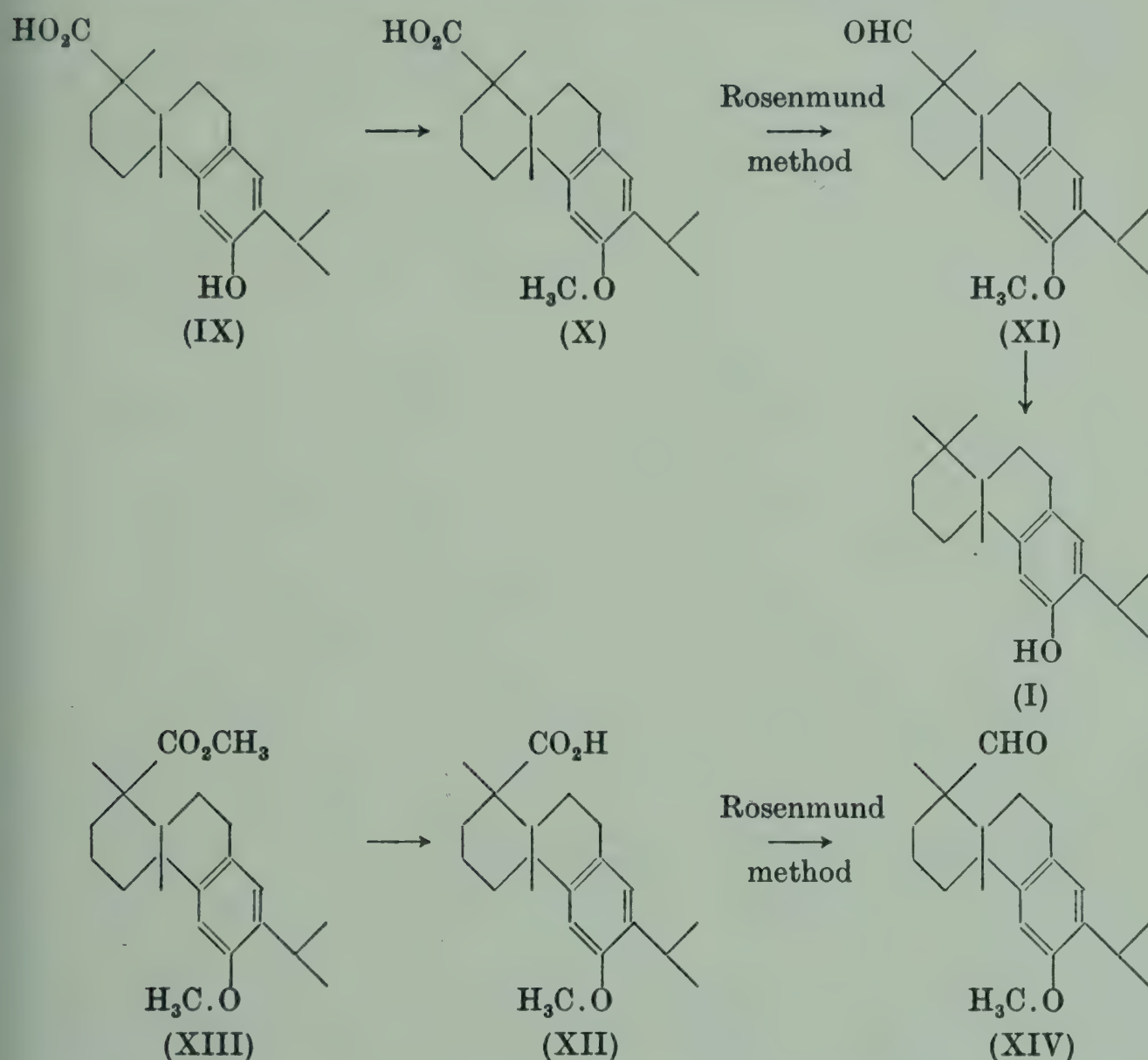


The experimental facts summarised above suggested that the formula (I) correctly represented ferruginol, and this has been confirmed by Campbell and Todd† by the partial synthesis of ferruginol, (a) from 6-*hydroxydehydroabietic acid*, and (b) from 7-*isopropylpodocarpic acid methyl ether*. 6-Hydroxydehydroabietic acid (IX) (see p. 422) was methylated to give 6-*methoxydehydroabietic acid* (X), m.p. 202.5–203.5°, which was reduced by the Rosenmund method to 6-*methoxydehydroabietinal* (XI), m.p. 137–138°, $[\alpha]_{H_g}^{28^\circ} + 90.3^\circ$ (in alcohol), *semicarbazone*, m.p. 236–237°. The latter semicarbazone afforded ferruginol (I) by heating with sodium ethoxide. In the alternative method of synthesis 7-*isopropylpodocarpic acid methyl ether* (XII), m.p. 183.5–184°, $[\alpha]_{H_g}^{28^\circ} + 150^\circ$ (in alcohol), prepared from *methyl 7-isopropylpodocarpate methyl ether* (XIII) (see p. 474), was similarly reduced by the Rosenmund method to 7-*isopropyl-*

* *J. Amer. C.S.* 1940, 62, 1287.

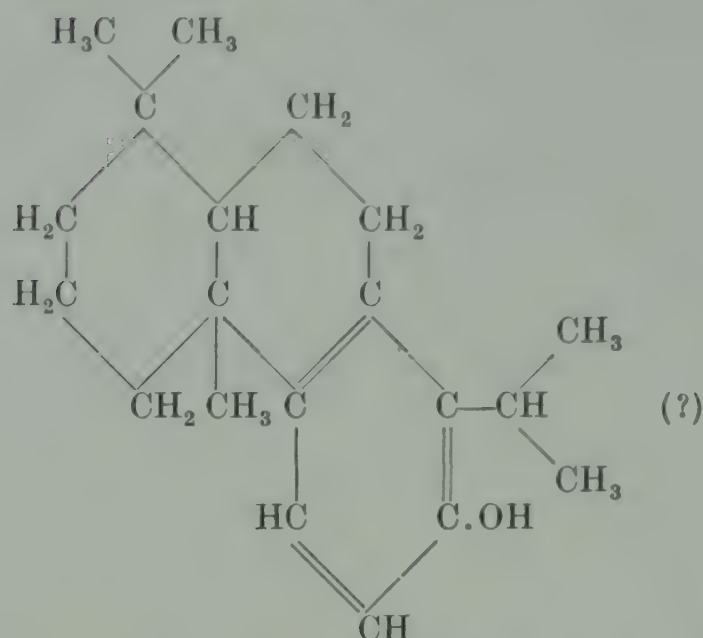
† *Ibid.* 1942, 64, 928.

podocarpinal methyl ether (XIV), m.p. $136-136.5^{\circ}$, from which, by the action of sodium ethoxide on the semicarbazone, ferruginol (I), was likewise obtained. These reactions can be summarised in accordance with the appended scheme, the stereochemical differences between the starting materials in these two syntheses being discussed further on pp. 474, 475.



Ferruginol can be readily characterised by the preparation of the *formate*, m.p. $96-97^{\circ}$, the *acetate*, m.p. $81-82^{\circ}$, $[\alpha]_D^{16} + 60.3^{\circ}$ (in alcohol) and the *benzoate*, m.p. 154° .

TOTAROL



The tricyclic diterpenoid phenol, *totarol*, $C_{20}H_{30}O$, m.p. 132° , $[\alpha]_D^{20} + 41.34^{\circ}$ (in alcohol), was first isolated by Easterfield and McDowell* from the wood of the totara tree (*Podocarpus Totara*), which is endemic to New Zealand.

Totarol gives a *formate*, m.p. 125.5° , an *acetate*, m.p. 121.5° , $[\alpha]_D^{18} + 44.58^{\circ}$ (in ether), and a *methyl ether*, m.p. $92-92.5^{\circ}$, $[\alpha]_D^{18} + 41.95^{\circ}$ (in ether). Its chemistry was first investigated by Short and Stromberg,[†] who showed that on catalytic hydrogenation a saturated hydrocarbon, *totarane*, $C_{20}H_{36}$, m.p. $74.5-75^{\circ}$, $[\alpha]_D^{20} - 31.06^{\circ}$ (in ether), was produced, which gave 1-methyl-8-isopropylphenanthrene (I), m.p. 102° , on dehydrogenation.[‡] Dehydrogenation of totarol itself afforded 7-hydroxy-1-methylphenanthrene (II), m.p. $190-191^{\circ}$, *acetate*, m.p. $133.5-136^{\circ}$, *methyl ether*, m.p. $133.5-134.5^{\circ}$.[§] Although Short and Stromberg^{||} originally regarded totarol as an alcohol, a recent investigation by Brandt and Thomas[¶] of its absorption spectrum and of its capacity for coupling with diazotised *p*-nitraniline has revealed that it is actually a phenol. The most likely formula would appear therefore to be that shown in (III), although this does not obey the isoprene rule.

On catalytic hydrogenation totarol is said to give, beside the saturated hydrocarbon totarane mentioned above, *dihydro-totarol*, $C_{20}H_{32}O$, m.p. $151-151.5^{\circ}$, $[\alpha]_D^{20} + 20.1^{\circ}$ (in ether),

* *Trans. New Zealand Inst.* 1911, **43**, 55; 1915, **48**, 518.

† *J.C.S.* 1937, p. 516.

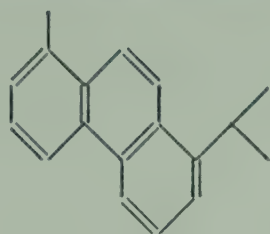
‡ Short and Wang, *ibid.* 1950, p. 991.

§ Short, Stromberg and Wiles, *ibid.* 1936, p. 319.

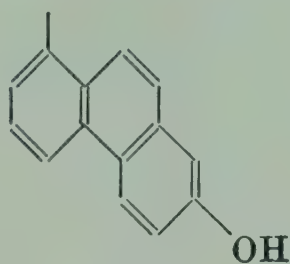
|| *Loc. cit.*

¶ Private communication.

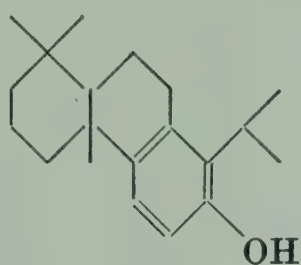
formate, m.p. $104.5-105^\circ$, which on further reduction yielded *tetrahydrototarol*, $C_{20}H_{34}O$, m.p. 134.5° , one of the ethylenic linkages proving resistant to hydrogenation.



(I)

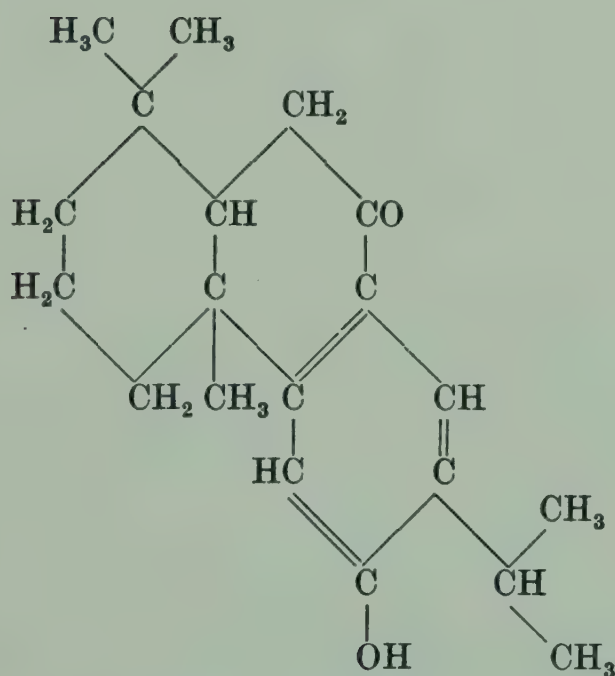


(II)



(III)

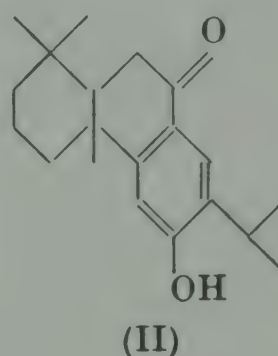
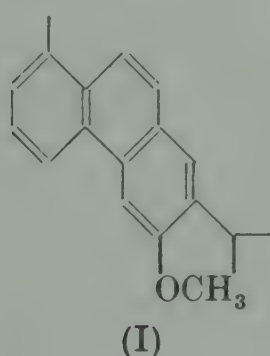
SUGIOL



The phenolic ketone, *sugiol*, $C_{20}H_{28}O_2$, m.p. $283-284^\circ$, $[\alpha]_D^{18} + 34.4^\circ$ (in pyridine), *acetate*, m.p. $164.5-165^\circ$, $[\alpha]_D^{17.5} + 26.7^\circ$, *benzoate*, m.p. $185.5-186.5^\circ$, $[\alpha]_D^{24} + 29.6^\circ$ (in pyridine), *methyl ether*, m.p. 137° , $[\alpha]_D^{24} + 31.5^\circ$ (in methanol), was isolated by Keimatsu, Ishiguro and Fukui* from *Cryptomeria japonica* D. Don. The presence of a ketonic function was established by the formation of an *oxime*, decomp. 176.5° and a *semicarbazone*, decomp. 246° , from *sugiol* and of an *oxime*, decomp. 166° and a *semicarbazone*, decomp. 254° , from *sugiol methyl ether*.

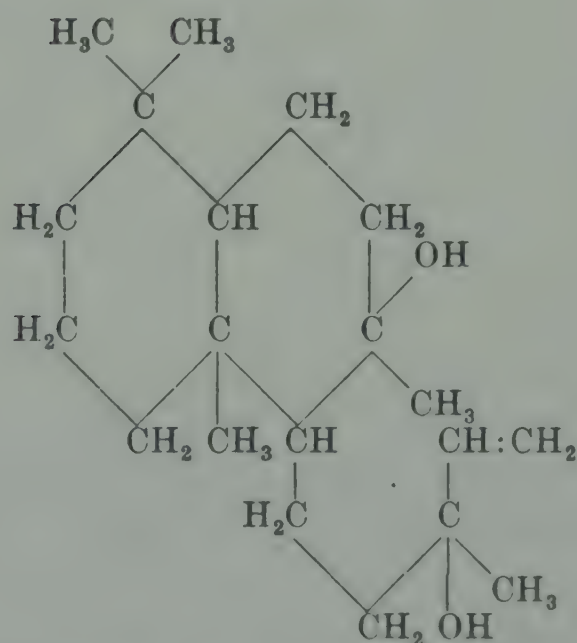
* *J. Pharm. Soc. Japan*, 1937, **57**, 92; *Chem. Zent.* 1937, **II**, 596.

Some progress was made towards the elucidation of the structure of sugiol by Huzii and Tikamori.* From the molecular formula and the established presence of one phenolic hydroxyl and one ketonic oxygen sugiol must be tricyclic. This was confirmed by submitting sugiol methyl ether to Clemmensen reduction and dehydrogenating the product, b.p. 165–175°/0.5 mm., to give 6-methoxyretene (I), m.p. 80°, derived *quinone*, m.p. 208.5° (*quinoxaline* derivative, m.p. 195–196°), identical with the methoxyretene obtained under similar conditions from hinokiol (p. 366). In spite of this relationship sugiol is not identical with hinokione. Recently Brandt and Thomas† have isolated 9-ketoferruginol (II) from the wood of the rimu tree (*Dacrydium cupressinum*) and have shown that it is identical with sugiol.



D. GLYCOL

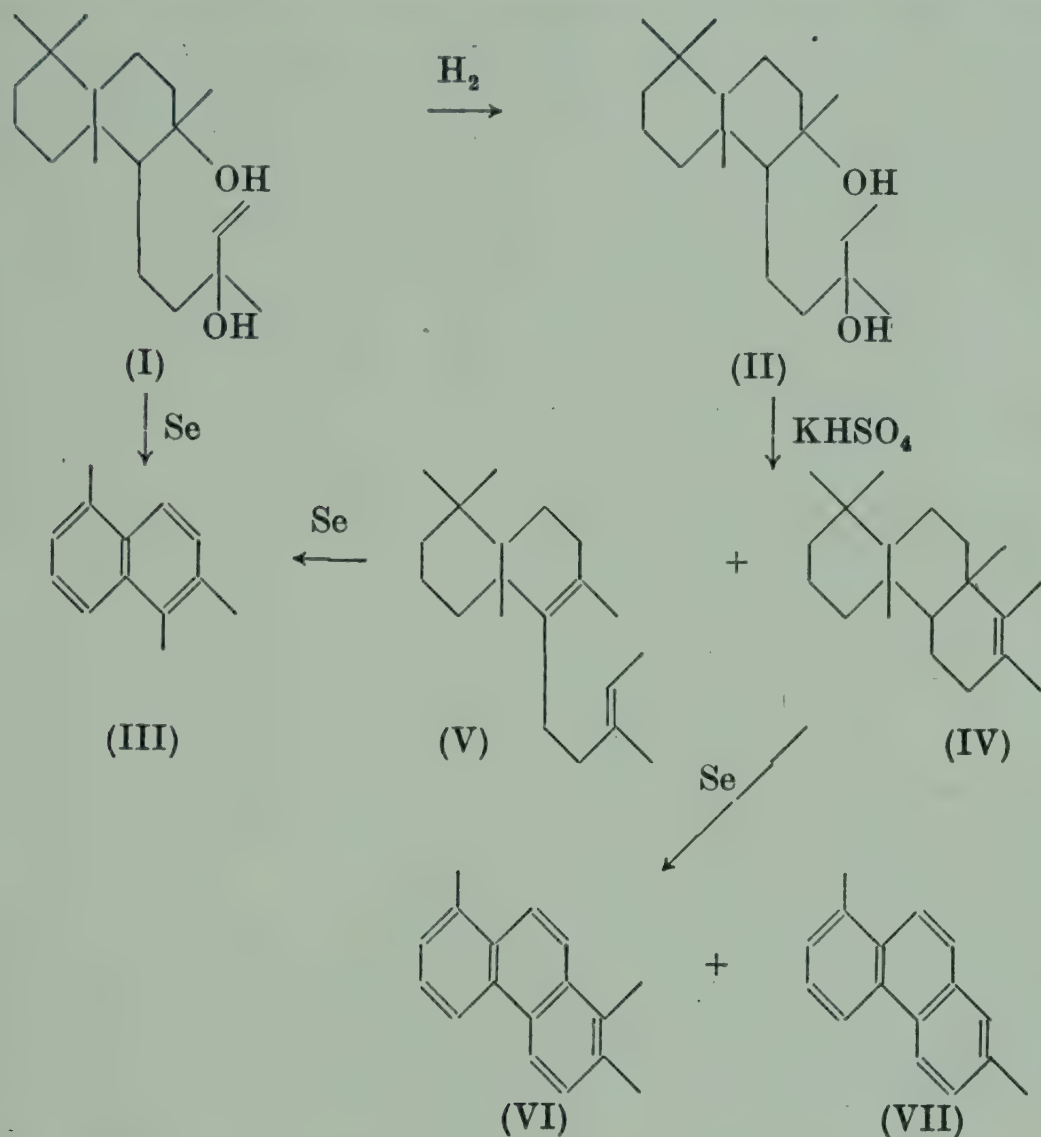
SCLAREOL



* *J. Pharm. Soc. Japan*, 1939, 59, 124; *Amer. Chem. Abs.* 1939, 33, 4592.

† Private communication; we are indebted to Mr Thomas for providing us with a copy of his paper on this subject prior to publication.

The bicyclic, diterpene ditertiary alcohol, *sclareol*, $C_{20}H_{36}O_2$ (I), m.p. $105.5-106^\circ$, b.p. $163-165^\circ/0.25$ mm., $d_4^{110^\circ} 0.9568$, $n_D^{104^\circ} 1.4858$, $n_D^{115^\circ} 1.4821$, $[\alpha]_D -3.3^\circ$ (in chloroform), was first isolated by Volmar and Jermstad* from the leaves of *Salvia Sclarea* L. Sclareol was recognised as a diterpene derivative by Janot† who



showed, also, by catalytic reduction to the saturated *dihydrosclareol*, $C_{20}H_{38}O_2$ (II), m.p. $114-115^\circ$, $[\alpha]_D -10.1^\circ$ (in chloroform), that it must be bicyclic and contain only one ethylenic linkage. The carbon skeleton of sclareol was partially characterised by the observation of Ruzicka and Janot‡ that sclareol gave 1:5:6-trimethylnaphthalene (III) on dehydrogenation with selenium.

When dihydrosclareol was heated with potassium bisulphate, *dihydrocyclosclarene*, $C_{20}H_{34}$ (IV), b.p. $142-145^\circ/0.5$ mm., $d_4^{21^\circ} 0.9335$, $n_D^{20^\circ} 1.5089$, contaminated with some *dihydroscclarene* (V),

* *Compt. rend.* 1928, 186, 517, 783.

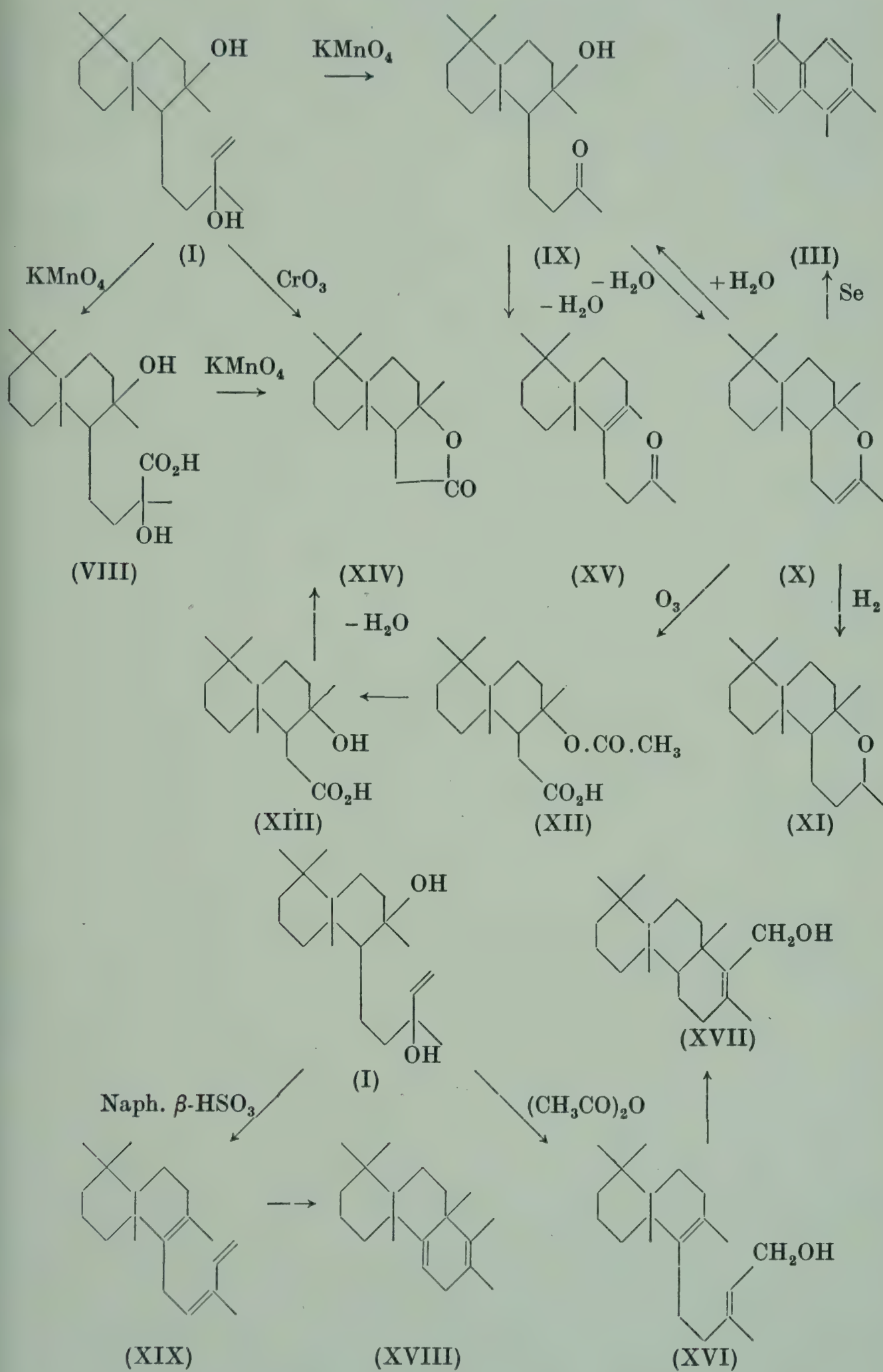
† *Ibid.* 1930, 191, 847; *ibid.* 1931, 192, 845.

‡ *Helv. Chim. Acta*, 1931, 14, 645; compare Janot, *Ann. Chim.* 1932 [x], 17, 5.

was formed. This impure dihydrocyclosclarene furnished a mixture of 1:7:8-*trimethylphenanthrene* (VI), m.p. 144–145°, *pimanthrene* (VII) and 1:5:6-*trimethylnaphthalene* (III), principally the first-named substance, on dehydrogenation with selenium. The naphthalene hydrocarbon (III) was derived, in all probability, from the uncyclised dihydrosclarene (V). The isolation of the 1:7:8-*trimethylphenanthrene* suggested that the carbon skeleton of sclareol was the same as that in agathenedicarboxylic acid (p. 459) and in manoyl oxide (p. 368).

The presence of a methylene side chain in sclareol was shown by ozonolysis, when formaldehyde was produced, and by oxidation with potassium permanganate, when an *acid*, $C_{19}H_{34}O_4$ (VIII) (p. 363), m.p. 153–154°, *methyl ester*, m.p. 111–112°, an unstable *ketone*, $C_{18}H_{32}O_2$ (IX), m.p. 91–92° and, after dehydration by heating *in vacuo*, an unsaturated *oxide*, $C_{18}H_{30}O$ (X), b.p. 174–176°/10 mm., were obtained.* The relationship between the unsaturated oxide and the ketone was established by the observation that they both gave the same *semicarbazone*, m.p. 145°, and were interconvertible by dehydration and by hydration respectively. On catalytic hydrogenation the oxide (X) furnished a mixture of two stereoisomeric *dihydro*-derivatives (XI), m.p. 83–84° and b.p. 118–120°/0.25 mm., and on dehydrogenation with selenium 1:5:6-*trimethylnaphthalene* (III) was produced. Further proof of the structure of (X) was provided by ozonolysis, when the *acetate* of a *hydroxy-acid*, $C_{18}H_{30}O_4$ (XII), m.p. 157–158°, resulted, yielding on hydrolysis the corresponding *hydroxy-acid* (XIII), m.p. 128–129°, from which a *lactone*, $C_{16}H_{26}O_2$ (XIV), m.p. 123–124°, $[\alpha]_D + 45.9^\circ$ (in chloroform) was easily prepared. This same lactone was also obtained by the oxidation of sclareol with chromic acid, or by oxidation of the acid (VIII), with potassium permanganate. When heated with alcoholic hydrobromic acid the lactone gave an isomeric *lactone*, $C_{16}H_{26}O_2$, m.p. 133–134°, $[\alpha]_D - 55.3^\circ$ (in chloroform). If the hydroxy-ketone (IX) was dehydrated by magnesium perchlorate in boiling toluene solution it afforded an unsaturated *ketone*, $C_{18}H_{30}O$ (XV), b.p. 130–135°/0.4 mm., *semicarbazone*, m.p. 197–198°, isomeric with the unsaturated oxide (X).

* Ruzicka and Janot, *loc. cit.*; Ruzicka, Seidel and Engel, *Helv. Chim. Acta*, 1942, 25, 621.



Recently Lederer and Mercier* have shown that the lactone (XIV) is identical with an oxidative degradation product from the triterpenoid ambrein. The oxidation products of sclareol have been investigated in more detail by Stoll and his collaborators† and a further correlation with ambrein has been established.

On digestion with acetic anhydride sclareol furnished a bicyclic primary *alcohol*, $C_{20}H_{34}O$ (XVI), b.p. $140^{\circ}/0.1$ mm., $d_4^{24^{\circ}}$ 0.9805, *acetate*, b.p. $170-173^{\circ}/0.3$ mm., $d_4^{23^{\circ}}$ 0.9915, $n_D^{23^{\circ}}$ 1.5060, containing two ethylene links. The formation of this alcohol from sclareol must involve a simultaneous dehydration and allylic rearrangement. If the acetate of (XVI) was heated with formic acid a monounsaturated, tricyclic primary *alcohol*, $C_{20}H_{34}O$ (XVII), b.p. $152^{\circ}/0.9$ mm., $d_4^{93^{\circ}}$ 0.985, $n_D^{93^{\circ}}$ 1.510, was obtained.

When sclareol was dehydrated by heating with naphthalene- β -sulphonic acid the triply unsaturated, bicyclic, *sclarene*, possibly (XIX), b.p. $125-128^{\circ}/0.2$ mm., $d_4^{17^{\circ}}$ 0.9388, $n_D^{17^{\circ}}$ 1.5217, resulted, and this was isomerised by digestion with formic acid to the tricyclic hydrocarbon, *cyclosclarene* (possibly (XVIII)), b.p. $118-120^{\circ}/0.2$ mm., $d_4^{22^{\circ}}$ 0.9455, $n_D^{22^{\circ}}$ 1.5176. This cyclic hydrocarbon, or a corresponding mixture of double bond isomers, was also obtained as a by-product when sclareol was digested with acetic anhydride.

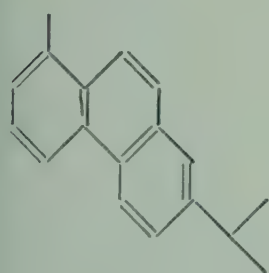
* *Exper.* 1947, **3**, 188.

† Stoll and Hinder, *Helv. Chim. Acta*, 1950, **33**, 1251; Hinder and Stoll, *ibid.* 1308; Lederer and Stoll, *ibid.* 1345.

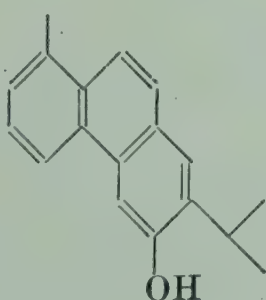
E. PHENOLIC ALCOHOL

HINOKIOL

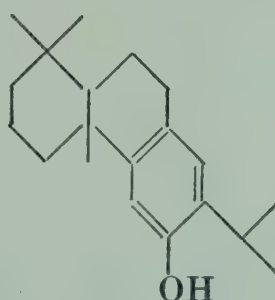
The diterpenoid phenolic alcohol *hinokiol*, $C_{20}H_{30}O_2$, m.p. 234–235°, b.p. 240–247°/5 mm., $[\alpha]_D^{20} + 74.4^\circ$, was first isolated by Yoshiki and Ishiguro* as one of the crystalline constituents present in the resin extracted from the heart wood of *Chamaecyparis obtusa* Sieb. et Zucc. Both oxygen atoms were present as esterifiable hydroxyl groups as was shown by the formation of a *diacetate*, m.p. 143°, $[\alpha]_D^{24} + 70.4^\circ$, a *dibenzoate*, m.p. 207°, $[\alpha]_D^{22} + 93.8^\circ$, and a *diphenylurethane*, $C_{34}H_{40}O_4N_2$, m.p. 246–247°. The chemistry of hinokiol has been extensively studied by Yoshiki and Ishiguro,† Keimatsu and Ishiguro,‡ and by Huzii and Tikamori.§ On dehydrogenation by heating with selenium hinokiol furnished retene (I), a *dihydroxyretene*, $C_{18}H_{18}O_2$, m.p. 234–235°, *diacetate*, m.p. 174°, *dibenzoate*, m.p. 203–204°, *diacetate quinone*, m.p. 213°, *dihydroxy quinone*, m.p. 297–299°, *dimethyl ether*, m.p. 173°, *dimethyl ether quinone*, m.p. 239–240°, *picrate*, m.p. 175–176°, which is still of unknown structure, and a *hydroxyretene*, m.p. 179–180°, *acetate*, m.p. 94°, *methyl ether*, m.p. 80°, *acetate quinone*, m.p. 190° (*quinoxaline derivative*, m.p. 194°), *hydroxy quinone*, m.p. 308° (*quinoxaline derivative*, m.p. 223°), *methyl ether quinone*, m.p. 208° (*quinoxaline derivative*, m.p. 193–196°). The latter was at first thought to be alcoholic in character but was subsequently shown by Brandt and Neubauer|| to be identical with the phenol obtained by dehydrogenation of ferruginol (see p. 356) and which was later identified by Campbell and Todd¶ as reten-6-ol (II).



(I)



(II)



(III)

+ *sec.* OH* *J. Pharm. Soc. Japan*, 1933, **53**, 11; *Chem. Zent.* 1933, **I**, 3203.† *Loc. cit.*‡ *J. Pharm. Soc. Japan*, 1935, **55**, 45; *Chem. Zent.* 1935, **II**, 3664.§ *J. Pharm. Soc. Japan*, 1939, **59**, 1116.|| *J.C.S.* 1939, p. 1031.¶ *J. Amer. C.S.* 1940, **62**, 1287.

Reten-6-ol has also been obtained from hinokiol by two other, less direct, routes. When hinokiol was distilled with zinc dust or copper bronze it afforded the phenolic ketone, *hinokione*, $C_{20}H_{28}O_2$, m.p. 188–189°, $[\alpha]_D^{20} + 103.4^\circ$, *acetate*, m.p. 119°, $[\alpha]_D^{19} + 105.3^\circ$, *semicarbazone*; decomp. 248–249°, *methyl ether*, m.p. 126–127°, $[\alpha]_D^{23} + 119.9^\circ$ (*semicarbazone*, decomp. 100–102°). Clemmensen reduction of hinokione followed by selenium dehydrogenation furnished reten-6-ol, whilst similar treatment of hinokione methyl ether gave 6-methoxyretene.

The experiments recorded above show that hinokiol has the carbon skeleton of the retene type of diterpenoids and that one of the oxygen atoms is present as a phenolic grouping at C_6 , and the other as a secondary alcohol. This evidence is summarised by the formula (III). The presence of the phenolic hydroxyl was confirmed by the preparation of a *monomethyl ether*, m.p. 95–96°, $[\alpha]_D^{18} + 59.5^\circ$ (*acetate*, m.p. 138°, $[\alpha]_D^{23} + 78.9^\circ$). The secondary nature of the alcoholic grouping was similarly confirmed by the facts that hinokione gave hinokiol and *isohinokiol*, $C_{20}H_{30}O_2$, m.p. 203–204°, $[\alpha]_D^{16} + 46.9^\circ$, *diacetate*, m.p. 65–67°, $[\alpha]_D^{16} + 45.3^\circ$, on catalytic hydrogenation in neutral solution, whilst hinokione methyl ether afforded hinokiol methyl ether and *isohinokiol methyl ether*, m.p. 118–119°, $[\alpha]_D^{20} + 42.9^\circ$, *acetate*, m.p. 168–169°, $[\alpha]_D^{23} + 11.8^\circ$, under the same conditions.

The oxidation of hinokiol derivatives has not so far given any conclusive evidence as to the position of the secondary hydroxyl group. Hinokiol methyl ether, on treatment with potassium permanganate in acetone solution, furnished *ketohinokiol methyl ether*, $C_{21}H_{30}O_3$, m.p. 160°, $[\alpha]_D^{21} + 25.9^\circ$, *acetate*, m.p. 121°, $[\alpha]_D^{23} + 54.4^\circ$, *benzoate*, m.p. 214°, *semicarbazone*, $C_{22}H_{33}O_3N_3$, decomp. 221–222°, oxidised further by chromic acid in acetic acid solution to *ketohinokione methyl ether*, $C_{21}H_{28}O_3$, m.p. 171–172°, $[\alpha]_D^{22} + 11.1^\circ$, in which the two keto groups are not in the α -position with respect to each other. The latter substance was also obtained more directly by chromic acid oxidation of hinokione methyl ether; it gave a *disemicarbazone*, $C_{23}H_{34}O_3N_6$, decomp. 229–230°. On catalytic hydrogenation ketohinokiol methyl ether or its acetate furnished hinokiol methyl ether or its acetate respectively. Catalytic hydrogenation of ketohinokione methyl ether, using a palladised charcoal catalyst, afforded

hinokione methyl ether, whilst a platinum catalyst gave a mixture of hinokiol and *isohinokiol* methyl ethers.

Comparable experiments with *isohinokiol* derivatives gave similar results. *isoHinokiol* methyl ether acetate was oxidised by chromic acid to *ketoisohinokiol methyl ether acetate*, $C_{23}H_{32}O_4$, m.p. 231–232°, $[\alpha]_D^{17} + 4.9^\circ$, hydrolysed by alkali to *ketoisohinokiol methyl ether*, m.p. 165–166°, $[\alpha]_D^{20} + 24.0^\circ$, which on further chromic acid oxidation gave ketohinokione methyl ether. Hydrogenation of *ketoisohinokiol* methyl ether, using a palladised charcoal catalyst, regenerated *isohinokiol* methyl ether.

From the above experiments it is seen that oxidation of hinokiol derivatives introduces a further ketonic oxygen atom which is readily replaced by hydrogen on catalytic hydrogenation.

Reduction of hinokiol with red phosphorus and iodine at 240–246° furnished an unsaturated *hydrocarbon*, $C_{19}H_{32}$ or $C_{20}H_{34}$, b.p. 330–335°, $d_4^{15} 0.9252$, $n_D^{20} 1.4999$, $[\alpha]_D^{15} + 5.5^\circ$, dehydrogenated by selenium to retene. If the reduction was carried out at 280–300° a saturated hydrocarbon, $C_{19}H_{34}$ or $C_{20}H_{36}$, b.p. 297–300°, $d_4^{15} 0.9200$, $n_D^{20} 1.4959$, $[\alpha]_D^{21} + 3.4^\circ$, resulted, which was also obtained by the further reduction of the unsaturated hydrocarbon in the same manner.

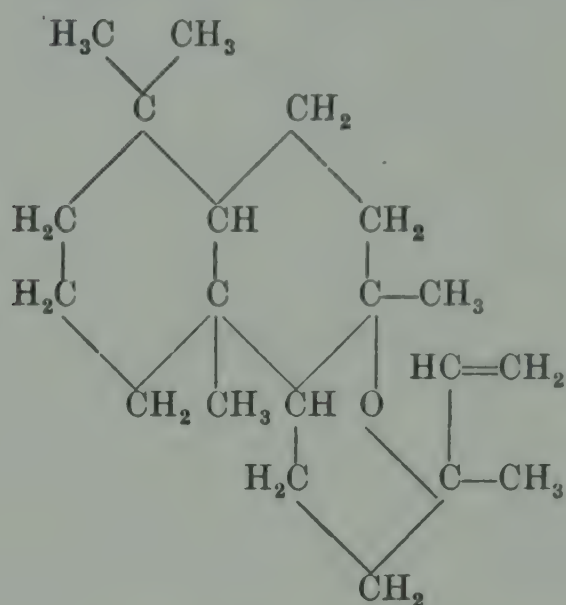
A by-product in the selenium dehydrogenation of hinokiol mentioned above was a *hydroxy compound*, $C_{18}H_{20}O$, m.p. 201–202°, *acetate*, m.p. 170°, *methyl ether*, m.p. 114°, *acetate quinone*, m.p. 216° (*quinoxaline derivative*, m.p. 188°), *hydroxy quinone*, m.p. 308° decomp., of unknown constitution.

Hinokione itself has also been identified as a constituent of the resin of *Chamaecyparis obtusa* Sieb et Zucc.

CHAPTER III

OXIDE

MANOYL OXIDE



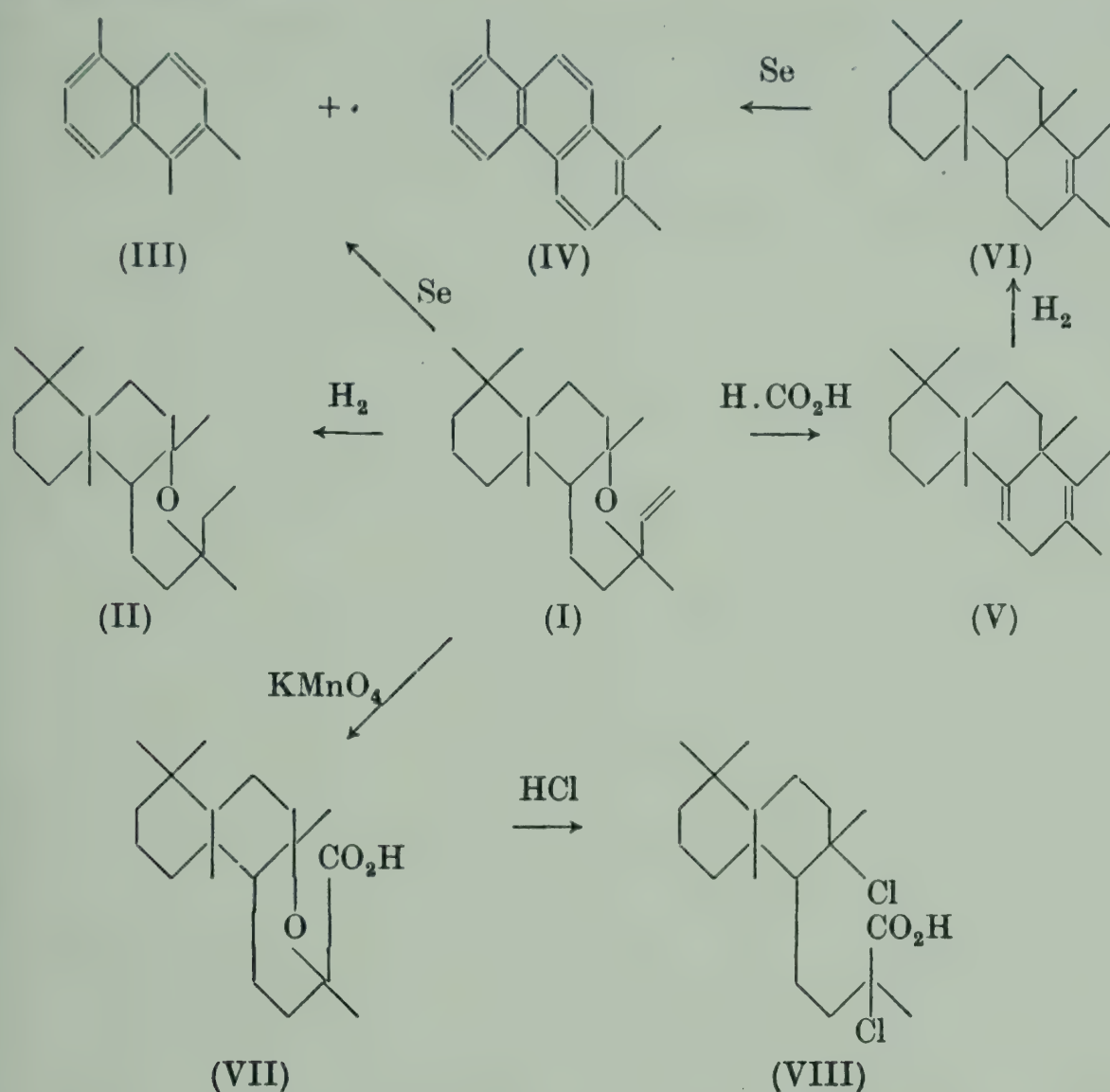
Hosking and Brandt* were the first to report the occurrence in nature of a diterpene oxide. They found that the wood oil of the silver pine (*Dacrydium Colensoi*; otherwise *D. westlandicum*) contained *manoyl oxide*, $C_{20}H_{34}O$, m.p. 29° , b.p. $135\text{--}137^\circ/0.3$ mm., $d_4^{16^\circ}$ 0.9858, $n_D^{16^\circ}$ 1.5130, $[\alpha]_D^{13^\circ} + 19.6^\circ$ (in alcohol) and were able to show† that this oxide must be represented by (I).

Manoyl oxide contained one ethylenic linkage, since it gave on catalytic hydrogenation *dihydromanoyl oxide*, $C_{20}H_{36}O$ (II), m.p. 19° , b.p. $148^\circ/0.2$ mm., $d_4^{16^\circ}$ 0.9758, $n_D^{16^\circ}$ 1.5052. The oxygen being completely inert suggested that it was probably present as a part of an oxide ring. Evidence for the carbon skeleton was obtained by dehydrogenation with selenium when a mixture of 1:5:6-trimethylnaphthalene (III) and 1:7:8-trimethylphenanthrene (IV) was obtained. Further when manoyl oxide was digested with formic acid it lost water to give a doubly unsaturated tricyclic hydrocarbon, *isomanoene*, $C_{20}H_{32}$, probably (V), b.p. $139\text{--}140^\circ/0.2$ mm., $d_4^{15^\circ}$ 0.9519, $n_D^{15^\circ}$ 1.5199, which could be partially hydrogenated to *dihydroisomanoene*, $C_{20}H_{34}$ (VI), $d_4^{18^\circ}$ 0.9354, $n_D^{18^\circ}$ 1.5098. This latter substance afforded on de-

* *Ber.* 1934, **67**, 1173; compare *idem*, *New Zealand J. Sci. Tech.* 1936, **17**, 750.

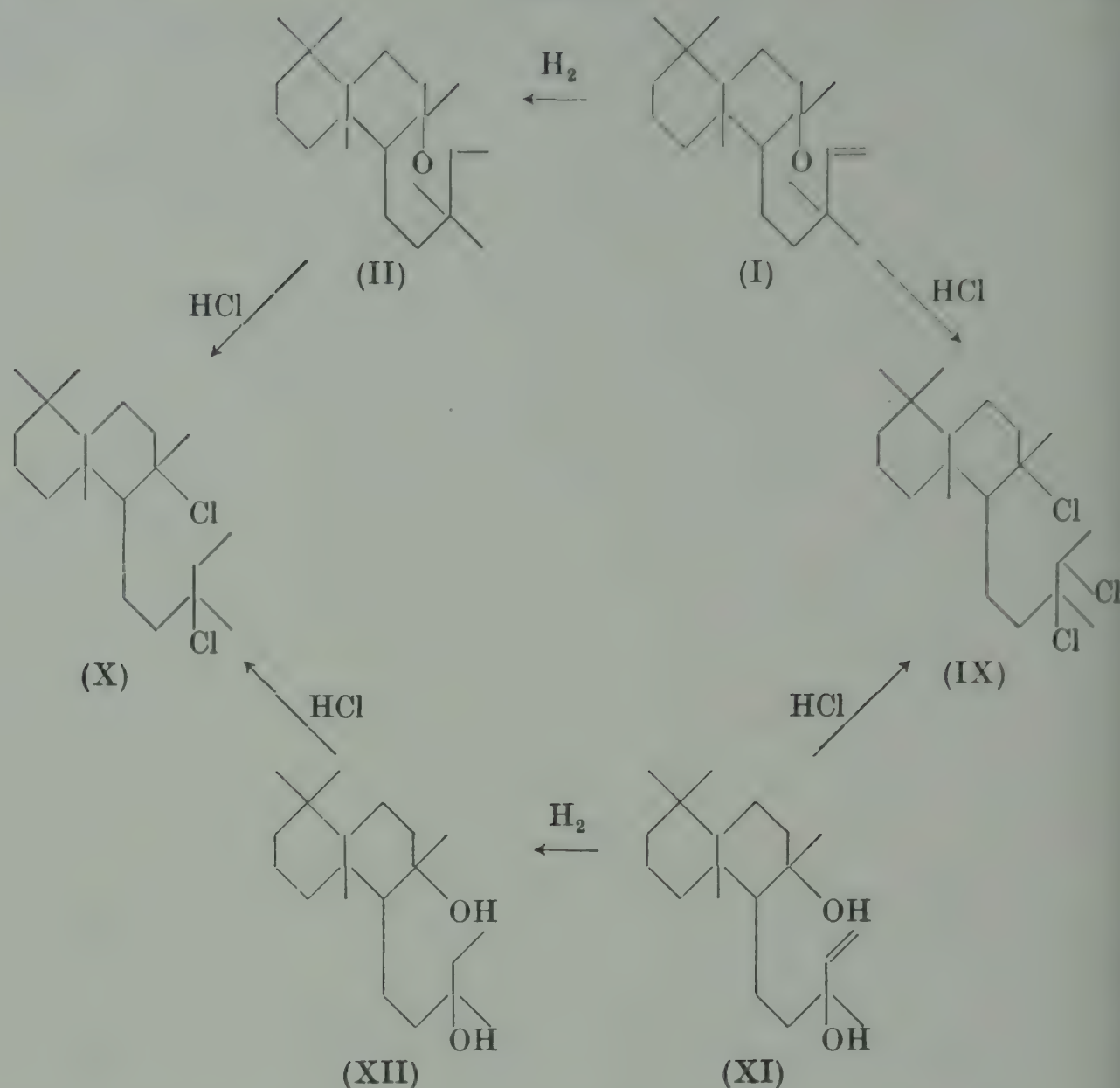
† *Ber.* 1935, **68**, 37; 1936, **69**, 780.

hydrogenation with selenium the same mixture of hydrocarbons as the parent oxide.



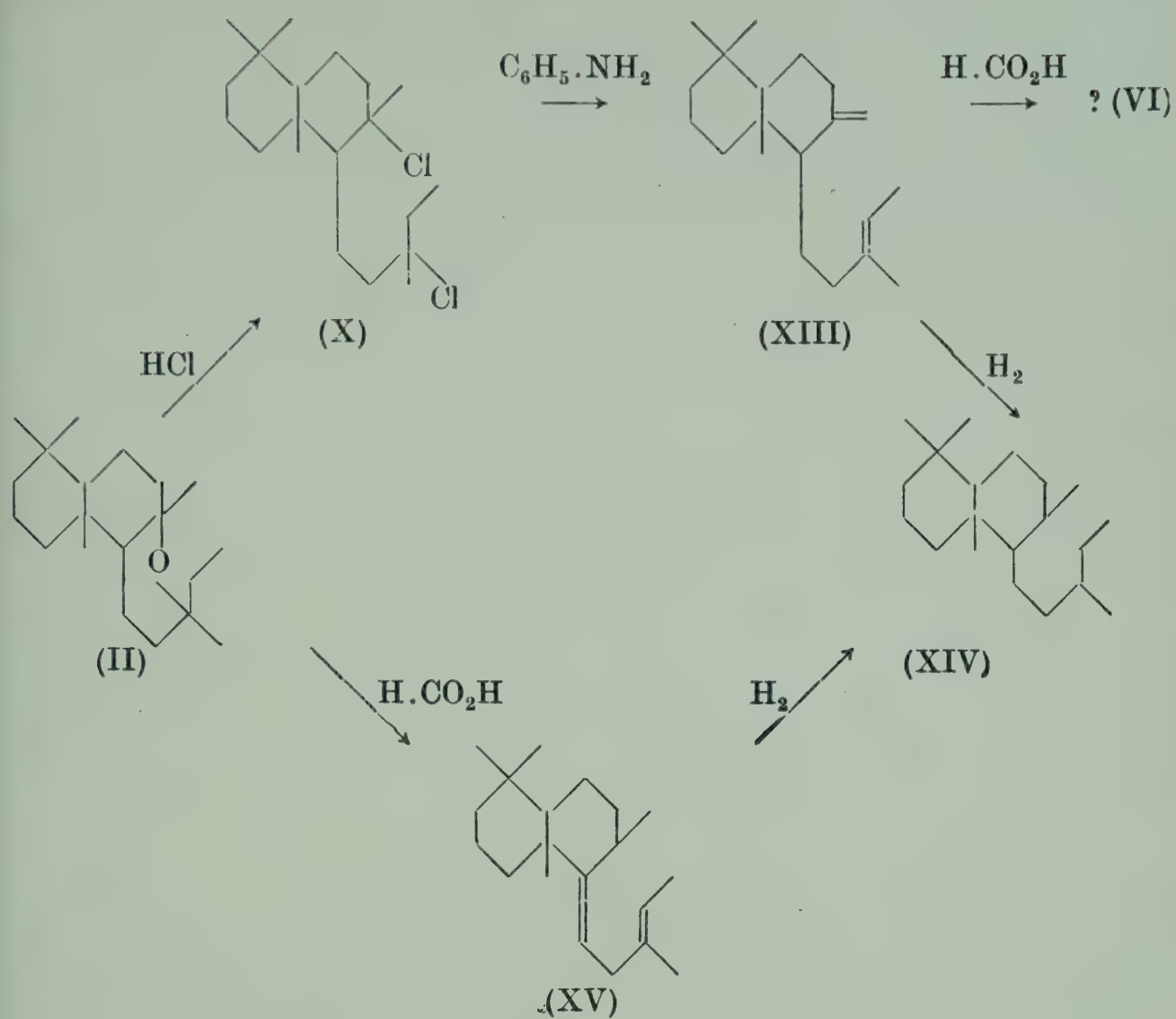
The presence of the exocyclic methylene group in manoyl oxide was proved by its ozonolysis when formaldehyde was obtained, and by oxidation with potassium permanganate when it gave an *acid*, $\text{C}_{19}\text{H}_{32}\text{O}_3$ (VII), m.p. $74-75^\circ$. Fission of the oxide ring in this acid occurred when it was treated with hydrogen chloride in ethereal solution, the *dihydrochloride*, $\text{C}_{19}\text{H}_{32}\text{O}_2\text{Cl}_2$ (VIII), m.p. $133-134^\circ$, being formed.

Valuable confirmatory evidence that manoyl oxide and dihydromanoyl oxide had been correctly formulated was obtained by a study of their interaction with hydrogen chloride, when they furnished *manoene trihydrochloride* (IX), m.p. $118-120^\circ$ and *dihydromanoene dihydrochloride* (X), m.p. $120-122^\circ$, respectively. These two derivatives were found to be identical with those prepared by the action of hydrogen chloride on sclareol (XI) and dihydrosclareol (XII) (see p. 361). When dihydromanoene di-



hydrochloride or the corresponding *dihydrobromide*, m.p. 97° , was heated with aniline α -*dihydromanoene*, $C_{20}H_{34}$, probably (XIII), b.p. $149-150^\circ/0.3$ mm., $d_4^{21^\circ} 0.9206$, $n_D^{21^\circ} 1.5089$, was formed, yielding on catalytic hydrogenation *tetrahydro- α -dihydromanoene* (XIV), which was not isolated, and cyclised by digestion with formic acid to an *isodihydromanoene*, b.p. $124^\circ/0.2$ mm., $d_4^{17^\circ} 0.9391$, $n_D^{17^\circ} 1.5105$, which is possibly identical with (VI).

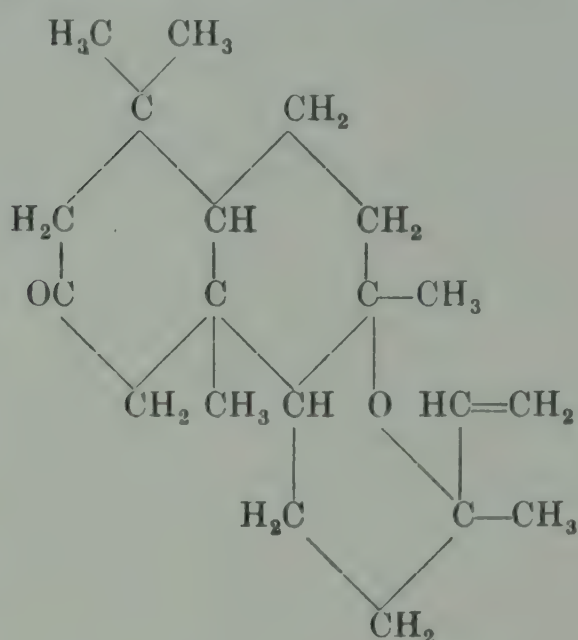
It was mentioned above that manoyl oxide gave on digestion with formic acid the tricyclic hydrocarbon, *isomanoene* (V). *Dihydromanoene* behaves in a somewhat similar manner, but it is not cyclised and yields the dicyclic unsaturated hydrocarbon, β -*dihydromanoene*, $C_{20}H_{34}$, possibly (XV), b.p. $123-124^\circ/0.2$ mm., $d_4^{19^\circ} 0.9164$, $n_D^{19^\circ} 1.5648$, readily reduced to the saturated hydrocarbon *tetrahydro- β -dihydromanoene*, $C_{20}H_{38}$, b.p. $145^\circ/0.1$ mm., possibly identical with (XIV).



CHAPTER IV

KETO-OXIDE

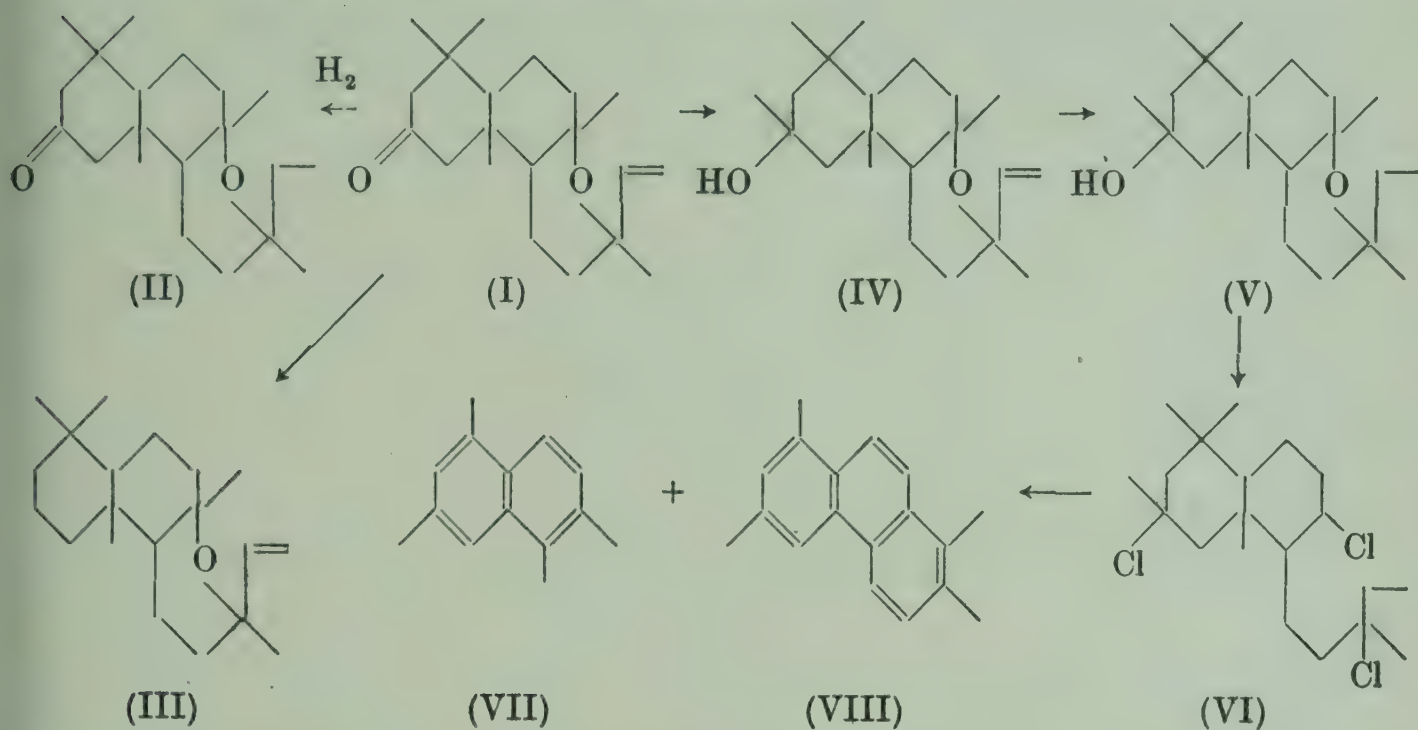
KETOMANOYL OXIDE



Ketomanoyl oxide, $C_{20}H_{32}O_2$ (I), m.p. $76-77^\circ$, b.p. $174-178^\circ/0.5$ mm., $[\alpha]_D^{13} + 40.4^\circ$ (in alcohol), characterised by the preparation of an *oxime*, m.p. $146-147^\circ$ and a *semicarbazone*, m.p. 135° , was isolated by Hosking and Brandt* from the wood oil of the silver pine (*Dacrydium Colensoi*; otherwise *D. westlandicum*). The presence of one ethylenic linkage in the ketone was proved by its catalytic hydrogenation to the saturated *dihydroketomanoyl oxide* (II), m.p. $89-90^\circ$, whilst its close relationship to manoyl oxide (III) was established by the preparation of the latter substance by heating the ketone semicarbazone with sodium ethoxide. The presence of a methylene group adjacent to the ketonic group in (I) followed from the formation of a liquid *hydroxymethylene* derivative, and the exact location of this keto group was elegantly demonstrated by the conversion of (I) to the *carbinol*, $C_{21}H_{36}O_2$ (IV), b.p. $151^\circ/0.2$ mm., by treatment with methyl magnesium iodide. This was reduced catalytically to the *dihydrocarbinol* (V), from which by the action of hydrogen chloride the trihydrochloride (VI) was prepared. By heating with aniline, hydrogen chloride was removed from this substance

* *Ber.* 1934, **67**, 1173; 1935, **68**, 286; *New Zealand J. Sci. Tech.* 1936, **17**, 750.

with formation of a triply unsaturated, bicyclic *hydrocarbon*, $C_{21}H_{34}$, b.p. $135^{\circ}/0.2$ mm., $d_4^{16^{\circ}}$ 0.9212, $n_D^{16^{\circ}}$ 1.5114, which on dehydrogenation with selenium afforded a mixture of 1:2:5:7-*tetramethylnaphthalene* (VII) and, probably, 1:2:6:8-*tetramethylphenanthrene* (VIII), *picrate*, m.p. 177° .



The experimental evidence outlined above leaves no doubt but that ketomanoyl oxide is correctly represented by the formula (I), already given.*

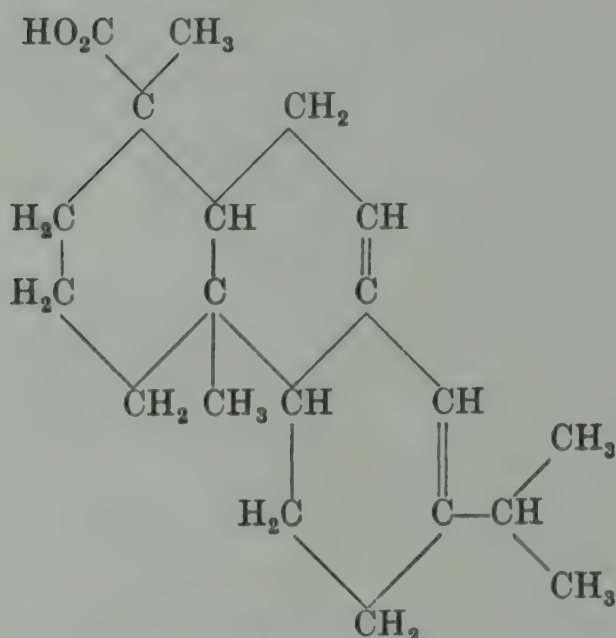
* Hosking, *Ber.* 1936, **69**, 780; Hosking and Brandt, *New Zealand J. Sci. Tech.* 1936, **17**, 750.

CHAPTER V

ACIDS

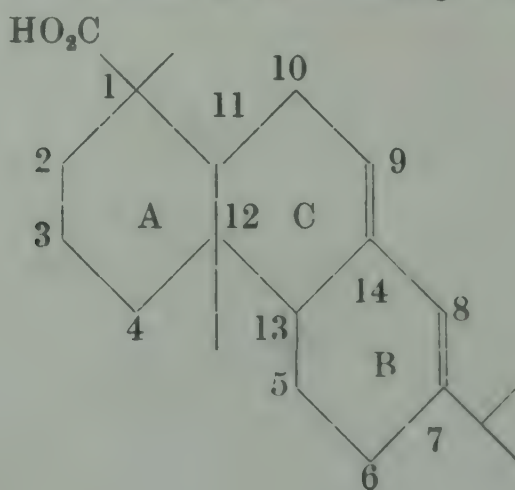
A. MONOCARBOXYLIC ACIDS

ABIETIC ACID*



Before discussing in detail the chemistry of abietic acid it is necessary, as a background to the subject, to give a brief account of the complex and confused history of the diterpenoid resin acids obtainable from conifers. When the bark of this type of tree is cut or damaged a semi-solid oleoresin or crude turpentine is slowly exuded. On standing, many of the oleoresins deposit semi-crystalline resin acids which can be separated and are then known as *galipot*. The best known galipot is the French variety

* The formula given below shows the numbering of the ring system.



obtained from the cluster pine (*Pinus Pinaster*; *Pinus maritima*) and is the usual source of *d*-pimaric acid (see p. 448). The oleo-resins are, as a rule, subjected to steam distillation yielding turpentine (Vol. II, p. 105) in the distillate, whilst a complex mixture of diterpenoid resin acids, *colophony* or *rosin*, remains behind in the still. The colophony is dried by a final heat treatment at about 160° and comes on to the market as a vitreous solid. Although colophony is mainly comprised of resin acids, it contains also a few per cent. of a neutral substance called *resene*.*

Fossil resins are formed when resin-exuding trees decay under anaerobic conditions. The copal and kauri copal of various tropical trees are obtained largely as fossilised material and yield the diterpenoid resin acid, *agathenedicarboxylic acid* (see p. 459). Many fossil resins from decayed pine trees have been examined and in the majority of cases the presence of *retene* and *fichtelite* (see p. 337) has been established.

Apparently Braconnet[†] was the first to recognise the acidic properties of colophony, but the isolation of a crystalline resin acid from this source by treatment with mineral acid was not effected until somewhat later by Riess.[‡] Baup[§] examined the resin of *Pinus Abies* and isolated a crystalline resin acid which he called *abietic acid*, but although this name has been retained in the literature Baup's acid was not homogeneous and did not correspond to the acid now known by this name. From the French colophony of *Pinus maritima* Baup obtained at the same time an amorphous resin acid, which he named *pininic acid*. In a comparable investigation Unverdorben^{||} separated from various resins an amorphous acid, which he also called *pininic acid*, and which he isomerised by hydrochloric acid to a crystalline acid, *sylvic acid*, probably roughly identical with the acid described earlier by Riess. Some doubt as to the nature of Unverdorben's pininic acid was raised by Rose,[¶] who considered

* *Inter al.* Tschirch and Studer, *Arch. Pharm.* 1903, **241**, 435; Paul, *Chem. Rev. Fette und Harzind.* 1915, **22**, 30; compare Herty and Williard, *Ind. Eng. Chem.* 1914, **6**, 895; Kesler, Lowy and Faragher, *J. Amer. C.S.* 1927, **49**, 2898.

† *Ann. Chim. Phys.* 1808, p. 67.

‡ *Jahrber. der polytechn. Inst. in Wien*, 1824, **1**, p. 435.

§ *Ann. Chim. Phys.* 1826, **31**, 108.

|| *Pogg. Annalen*, 1828, **11**, 27, 230, 393.

¶ *Ibid.* 1841, **53**, 383.

it to be simply autoxidised sylvic acid, whilst Maly* suggested, quite erroneously, that it might be abietic anhydride. Cailliot† separated from crude Strasburg turpentine a crystalline acid which he named abietic acid, but it was clearly not identical with the acid of Baup.

The name, *pimaric acid*, was introduced by Laurent‡ for a crystalline resin acid which he obtained from French colophony. By heat treatment Laurent isomerised his pimaric acid to a *pyromaric acid*, which he subsequently§ considered to be identical with the sylvic acid of Unverdorben, an opinion which was disputed by Siewert.|| Maly¶ undertook an extensive study of American colophony and obtained from this source an acid which he called abietic acid, although it differed in properties from acids previously described by that name. He claimed to have obtained the same acid from the resins of *Pinus Abies* and *Pinus Larix*, and claimed also that it was isomerised by mineral acids to sylvic acid. Flückiger,** by passing hydrogen chloride into an alcoholic solution of colophony, obtained a crystalline acid which he considered to be identical with Maly's abietic acid, obtained without an isomerising agent. Laurent's pimaric acid was further studied by Duvernoy,†† Dietrich,** Liebermann§§ and Haller,||| and whilst his original observations were, in general, confirmed, Liebermann concluded that colophony itself contained only sylvic acid and that all the abietic acids previously described were merely impure specimens of this acid. About 1885, therefore, it was generally recognised that there were two resin acids, the abietic acid or sylvic acid of American colophony and the pimaric acid obtainable from French galipot and colophony.

The investigations of Cailliot,¶¶ and more particularly of Vesterberg,*** on the nature of pimaric acid led to the recognition of the

* *Annalen*, 1864, 132, 249.

† *Jour. Pharm.* 1830, 16, 436.

‡ *Ann. Chim. Phys.* 1839 [ii], 72, 383; *Annalen*, 1840, 34, 272.

§ *Ann. Chim. Phys.* 1848 [iii], 22, 460; *Annalen*, 1848, 68, 335.

|| *Jahresber.* 1859, p. 509; *Zeit. für Naturwiss.* 1869, 14, 311.

¶ *J. pr. Chem.* 1862 [i], 86, 111; *Annalen*, 1864, 129, 94; 1864, 132, 249; 1868, 149, 244; 1872, 161, 115.

** *J. pr. Chem.* 1867 [i], 101, 235.

†† *Annalen*, 1868, 148, 143.

‡‡ *Thesis*, Berne, 1883.

§§ *Ber.* 1884, 17, 1885.

||| *Ibid.* 1885, 18, 2165.

¶¶ *Bull. Soc. chim.* 1874 [ii], 21, 387.

*** *Ber.* 1885, 18, 3331; 1886, 19, 2167; 1887, 20, 3248; 1903, 36, 4200; 1905, 38, 4125.

presence of two homogeneous acids, *d-pimaric acid* and *levo-pimaric acid* in French galipot.* This led to a considerable clarification of a confused field, but the true nature of abietic acid was only realised at a much later date and after much further misleading and incorrect work.

Tschirch and Studer[†] suggested that the abietic acid of American colophony was a mixture of three isomers, α -, β - and γ -*abietic acids*, but the evidence which they advanced in support of this view was slight.[‡]

Although Tromsdorff[§] and Liebig^{||} gave for the resin acids the correct empirical formula, and Duvernoy[¶] assigned to them the correct molecular formula, $C_{20}H_{30}O_2$, and was supported by other workers,** these proposals were not accepted without much dissent.^{††} However, the investigations of Vesterberg on the pimaric acids (see pp. 428 and 448) and of Fahrion^{**} and more especially of Levy^{§§} on abietic acid finally resulted in the general

* The history and chemistry of these two acids are dealt with in separate articles on pp. 447, and 428.

† *Arch. Pharm.* 1903, **241**, 495; compare Proth, *Schweiz Apoth. Ztg*, 1916, **54**, 196.

‡ Tschirch and Studer (*Die Harze*, Vol. I, pp. 261, 342) have listed a number of resin acids isolated by Tschirch and his collaborators which, since their homogeneity is extremely doubtful, have not been considered here. The acids listed below have also not been mentioned in the text, in spite of the fact that some progress had been made with their chemistry, as their homogeneity is now in considerable doubt: *Laricinolic acid* from larch turpentine (see Trost, *Ann. Chim. Appl.* 1935, **25**, 496); *canadolic acid* from Canada balsam (see Trost, *ibid.* 1936, **26**, 38); *densipimaric acid* from the Japanese pine (see Suzuki, *Sci. Pap. Inst. Phys. Chem. Res. Tokyo*, 1935, **26**, 98); *rubeabietic acid* from *Ceroplastes rubens* Mask. (see Kono and Maruyama, *J. Agric. C.S. Japan*, 1936, **12**, 512; 1938, **14**, 318) and *sandaracopimaric acid* from sandarac resin (see Balas and Brzak, *Coll. Czeck. Chem. Comm.* 1929, **1**, 306, 352). Furthermore, no account of the chemistry of pinabietic acid from tallöl (Aschan, *Annalen*, 1921, **424**, 117; Aschan and Ekholm, *ibid.* 1921, **424**, 133; Virtanen, *ibid.* 1921, **424**, 150; Aschan, *Ber.* 1922, **55**, 2944; Aschan and Levy, *ibid.* 1927, **60**, 1923; Aschan, *Fenno-Chem.* 1929, **1**, 18; *Annalen*, 1930, **483**, 124) is given here, for it has recently been shown by Hasselström, McPherson and Hopkins (*Paper Trade J.* 1940, **110**, No. 4, p. 41; compare Aschan and Levy, *loc. cit.*; Aschan, *Annalen*, 1930, **483**, 124; Ruzicka, Goldberg, Huyser and Seidel, *Helv. Chim. Acta*, 1931, **14**, 550) that it is merely a mixture of abietic acid, dehydroabietic acid, a dihydroabietic acid and *d*-pimaric acid.

§ *Annalen*, 1835, **13**, 169.

|| *Ibid.* 1835, **13**, 174.

¶ *Ibid.* 1848, **148**, 143.

** Siewert, *loc. cit.*; Strecker, *Annalen*, 1869, **150**, 131; Valente, *Atti R. Accad. Lincei*, 1884, **1**, 13; Bischoff and Nastvogel, *Ber.* 1890, **23**, 1919; Mead and Kremers, *Proc. Amer. Pharm. Assoc.* 1893, **41**, 198.

†† *Inter al.* Maly, *loc. cit.*; Emmerling, *Ber.* 1879, **12**, 1441; Dietrich, *Chem. Zent.* 1885, p. 886; Ducommon, *ibid.* 1885, p. 886; Mach, *Monatsh.* 1893, **14**, 187; 1894, **15**, 627; Tschirch and Studer, *Arch. Pharm.* 1903, **241**, 495.

** *Zeit. Angew. Chem.* 1901, **14**, 1197, 1221.

§§ *Ibid.* 1905, **18**, 1739; compare Klason and Kohler, *J. pr. Chem.* 1906 [ii], **73**, 337; Leskiewicz, *ibid.* 1910 [ii], **81**, 403.

acceptance of the molecular formula $C_{20}H_{30}O_2$ for the resin acids.

The interesting papers of Klason and Kohler* and of Kohler† introduced a classification of resin acids which had the merit of simplicity and which did much to stimulate further work in this field. A distinction was made between *primary resin acids*, present in the original oleoresin, and *secondary resin acids*, formed therefrom by the isomerising action of heat or acids, and it is still convenient to maintain such a differential nomenclature. It was considered that the primary resin acids comprised *d*-pimaric acid and levopimaric acid, which were fairly resistant to autoxidation and isomerisation by heat, and two hypothetical α - and β -*sapinic acids*, readily autoxidised and rearranged by mild heating. During the processing of the oleoresin to colophony it was thought that the primary acids, except *d*-pimaric acid, were isomerised to the laevorotatory α -*colophonic acid* and the dextrorotatory β -*colophonic acid*, the former having constants in rough agreement with those accepted at the time for abietic acid.

Schkateloff‡ undertook an extensive investigation of various conifer resins and claimed to isolate four acids, α -, β -, γ - and δ -*sylvic acids*. α -Sylvic acid, the primary resin acid, was rearranged by alcoholic sulphurous acid to β -sylvic acid which was probably an impure specimen of abietic acid. By distillation under reduced pressure both α - and β -sylvic acids afforded an optically inactive γ -sylvic acid, whilst from the mother liquors of the recrystallisation of this latter acid, δ -sylvic acid, possibly identical with *d*-pimaric acid, was obtained. Leskiewicz§ prepared what he considered to be a homogeneous primary resin acid, *sapinic acid*, from the oleoresin of *Pinus sylvestris* which, on treatment with hydrochloric acid in acetic acid or alcoholic solution was isomerised to a laevorotatory acid, *l*-sylvic acid. On distillation both *sapinic* and *l*-sylvic acids afforded an *l*-*colophonic acid* identical with the previously mentioned α -*colophonic acid* of Klason and Kohler.

Work in this field was continued by Dupont,|| who found that

* *J. pr. Chem.* 1906 [ii], 73, 337; *Arkiv. Kemi. Min. Geol.* 1905, 2, No. 3.

† *Arkiv. Kemi. Min. Geol.* 1910, 4, No. 5, p. 29; *J. pr. Chem.* 1912 [ii], 85, 534.

‡ *Chem. Zent.* 1908, I, 2097; II, 807.

§ *J. pr. Chem.* 1910 [ii], 81, 403.

|| *Compt. rend.* 1921, 172, 1373; *Bull. Soc. chim.* 1921 [iv], 29, 727.

levopimaric acid was isomerised by hydrochloric acid in alcoholic solution to give first α -pimarabietic acid and finally β -pimarabietic acid, recognised as identical with abietic acid. The intermediate α -acid was not however isolated. Later Dupont and Uzac* examined Aleppo galipot (from *P. halepensis*) and Dupont and Dubourg† the galipot of *P. Pinea*. From the former two impure acids, α - and β -alepic acids, were obtained, which could be isomerised *via* the hypothetical α - and β -alepabietic acids, to abietic acid. β -Alepic acid and the derived β -alepabietic acid were subsequently shown by Dupont‡ to be mixed crystals of α -alepabietic acid and abietic acid. From the galipot of *P. Pinea* Dupont and Dubourg separated an acid of the sapinic acid type,§ *pineic acid*, which they also isomerised to abietic acid possibly *via* α -alepabietic acid.

Based essentially on the changes in optical rotatory power observed during the isomerisation of levopimaric acid to abietic acid, Dupont and Uzac suggested that the following classification of resin acids was generally applicable.

Primary Resin acids	Secondary Resin acids	
	First stage	Second stage
	Not isomerised	
<i>d</i> -Pimaric acid		
Levopimaric acid	α -Pimarabietic acid	Abietic acid
α -Sapinic acid	α -Sapinabietic acid	Abietic acid
β -Sapinic acid	β -Sapinabietic acid	Abietic acid

At about the same time Aschan^{||} suggested a more complex classification of the resin acids into three main groups, the *natural resin acids*, which included the *pimaric acids* and the *sapinic acids*, the *colophonic acids*, consisting of *isopimaric acids*, formed by mild heating, and the *abietic acids* formed by stronger heating of the natural acids, and *sylvic acids* obtained by chemical rearrangement of these natural acids. He further divided the sapinic acids into *pininic acids* and *isopininic acids* depending on the temperature used in extracting the natural resin acids, and

* *Bull. Soc. chim.* 1924 [iv], 35, 394.

† *Ibid.* 1926 [iv], 39, 1029; *Bull. Inst. Pin.* 1926, p. 393; compare Reutter, *J. de Pharm. et de Chim.* 1912 [vii], 6, 494.

‡ *Bull. Soc. chim.* 1924 [iv], 35, 879; Dupont and Desalbres, *ibid.* p. 890; compare Rouin, *Bull. Inst. Pin.* 1928, p. 167.

§ Compare Aschan, *Finska Kemi. Medd.* 1923, 31, 70; 1923, 32, 75; Nordstrom, *J. pr. Chem.* 1929 [ii], 121, 204.

|| *Chem. Ztg.* 1924, 48, 149; *Naphthenverbindungen, Terpene und Campherarten*, 1929, p. 255.

the sylvic acids into *true* sylvic acids obtained by isomerising the other resin acids with mineral acid, and the *isosylvic acids*, obtained by dehydrohalogenation of the hydrogen halide addition products of these acids.

More recent work has now conclusively shown that these complicated systems of classification are quite unnecessary. The experiments of Hasselström and Bogert,* of Kraft,† of Harris‡ and of Lombard§ have demonstrated that the sapinic acids are mixtures of *d*-pimaric acid, *iso-d*-pimaric acid, levopimaric acid and neoabietic acid. Kraft|| claimed to have isolated from *Pinus Pinaster* an isomer of abietic acid, *proabietic acid*, m.p. 159–160°, $[\alpha]_D^{20} + 11.5^\circ$ (in alcohol), but this has now been shown by Harris and Sparks¶ to be a mixture. It has not therefore been listed as one of the primary resin acids in the table given below.**

The following classification†† of diterpenoid resin acids in which the term “primary” refers to those acids present in the original oleoresin, “secondary” to those formed therefrom by isomerisation and “tertiary” to those formed by loss or addition of hydrogen from or to the second group by the action of heat, is now suggested.

Primary Resin Acids††

d-Pimaric acid (see p. 447)

iso-d-Pimaric acid (see p. 457)

Levopimaric acid (see p. 428)

Neoabietic acid (see p. 445)

Dihydrolevopimaric acid (see p. 438)§§

* *J. Amer. C.S.* 1935, 57, 2118.

† *Annalen*, 1935, 520, 133; compare Vocke, *ibid.* 1933, 508, 11; Sandermann, *Ber.* 1938, 71, 2005; Arbusov, *Lesokhim. Prom.* 1940, 3, No. 5, p. 3.

‡ *J. Amer. C.S.* 1948, 70, 3671.

§ *Compt. rend.* 1944, 219, 587; *Bull. Soc. Chim.* 1945 [v], 12, 395.

|| *Annalen*, 1936, 524, 1.

¶ *J. Amer. C.S.* 1948, 70, 3674.

** Compare Sandermann, *Ber.* 1941, 74, 154.

†† Compare Harris, *loc. cit.*

§§ Although Wienhaus, Ritter and Sandermann (*Ber.* 1936, 69, 2198) have obtained abietic acid from the oleoresin of *Pinus sylvestris*, using only repeated recrystallisation from methanol, it cannot be assumed that this acid is a constituent of the oleoresin as exuded from the tree. It appears that isomerisation of the primary resin acids to abietic acid can be caused merely by digestion with methyl alcohol, as is known to be the case with aqueous ethyl alcohol (see p. 381 and compare Dupont, *Compt. rend.* 1921, 172, 1373).

§§ The dihydrolevopimaric acid whose presence has been detected among the primary resin acids (Fleck and Palkin, *J. Amer. C.S.* 1939, 61, 1230) is often referred to as a dihydroabietic acid. Since, however, it is undoubtedly present in the oleoresin as exuded from the tree, it has been decided here to indicate this relationship by referring it to levopimaric acid and not to abietic acid.

Secondary Resin Acids

Abietic acid

Tertiary Resin Acids

Dehydroabietic acid (see p. 413)

Dihydroabietic acids (see p. 417)

Tetrahydroabietic acid (see p. 418)

Two general methods have been used for the preparation of abietic acid. The first of these depends upon the isomerisation of the primary resin acids by heat, the second upon effecting this isomerisation by acids, suitably acetic or hydrochloric acids.

Maly* digested colophony with hot aqueous alcohol for many hours and recrystallised the product from the same solvent. This method was much used in the earlier investigations, but the yields were poor and the desired isomerisation can be carried out much more readily by distillation *in vacuo*, a process first introduced by Bischoff and Nastvogel† and later used by Easterfield and Bagley,‡ Levy,§ Ruzicka and Meyer,|| Rau and Simonsen,¶ and others. The distillation can also be effected by the use of superheated steam.** Very much more convenient than the distillation process is the method due to Steele,†† in which an acetic acid solution of colophony is boiled for some hours.

The isomerisation of the primary resin acids to abietic acid by the action of mineral acid, usually in alcoholic solution, has been studied by many workers. As examples of the more recent use of hydrochloric acid the work of Leskiewicz,‡‡ Schulz,§§ Dupont,||| Dupont and Uzac,¶¶ and Palkin and Harris,*** can be quoted, whilst Cohn††† has shown methanolic sulphuric acid to

* *J. pr. Chem.* 1862 [i], **86**, 111; *Annalen*, 1864, **129**, 94.

† *Ber.* 1890, **23**, 1919.

‡ *J.C.S.* 1904, **85**, 1238; compare Henry, *ibid.* 1901, **79**, 1144.

§ *Zeit. Angew. Chem.* 1905, **18**, 1739.

|| *Helv. Chim. Acta*, 1922, **5**, 315.

¶ *Ind. For. Rec.* 1925, **11**, 207.

** Johansson, *Arkiv. Kemi. Min. Geol.* 1917, **6**, No. 19; Wislicenus, Liang and Stelzer, *Zeit. Angew. Chem.* 1927, **40**, 1500.

†† *J. Amer. C.S.* 1922, **44**, 1333; compare Dupont, Desalbres and Bernette, *Bull. Inst. Pin.* 1926, **22**, 349; Dupont, *Bull. Soc. chim.* 1921 [iv], **29**, 718.

‡‡ *J. pr. Chem.* 1910 [ii], **81**, 403. §§ *Chem. Ztg.* 1917, **41**, 666.

||| *Bull. Soc. chim.* 1921 [iv], **29**, 727; 1924 [iv], **35**, 879.

¶¶ *Ibid.* 1924 [iv], **35**, 394.

*** *J. Amer. C.S.* 1934, **56**, 1935. For the description of a large-scale preparation by this method see Shkatelov, *Lesokhim. Prom.* 1934, **3**, 5.

††† *Chem. Ztg.* 1916, **40**, 791.

be effective. The abietic acid prepared by these methods is further purified by crystallisation. Thus a typical specimen of abietic acid prepared by vacuum distillation* had m.p. *ca.* 158° and $[\alpha]_D$ *ca.* -70° (in alcohol), whilst prepared by Steele's method (see below) an abietic acid, m.p. 159–161°, $[\alpha]_D$ -77.3° (in alcohol), was obtained.† A convenient procedure for the final purification of abietic acid is the "quarter sodium salt" method, which was first used systematically by Dupont, Desalbres and Bernette.‡ This salt, $(C_{20}H_{30}O_2)_3 \cdot C_{20}H_{29}O_2Na$, is crystalline and can be purified by recrystallisation. It is reasonably stable and thus serves as a method of storing the easily autoxidised abietic acid. However, at the present time the amine salt method, to which reference is made below, would appear to be the most convenient procedure for the purification of abietic acid.

Although Schulz§ is usually credited with obtaining the first specimen of pure abietic acid, m.p. 171–173°, $[\alpha]_D$ -96.8° (in alcohol), acids of equal purity were apparently obtained earlier by Leskiewicz|| and by Kohler,¶ since they had m.p. 171–172°, $[\alpha]_D$ -104.2° (in alcohol) and m.p. 166–173°, $[\alpha]_D$ -94.8° (in alcohol), respectively. Palkin and Harris** have made a careful study of the highly purified quarter sodium salt of abietic acid, for which they find m.p. 205–208°, $[\alpha]_D$ -95° (in alcohol), yielding on acidification pure abietic acid, m.p. 170–174°, $[\alpha]_D$ -102° (in alcohol).††

Abietic acid can also be obtained in a high state of purity by recrystallisation of its salts with aliphatic amines,** and

* Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 315.

† Somewhat higher rotations, -80° to 92° (in alcohol) are recorded by Ruzicka and Schinz (*Helv. Chim. Acta*, 1923, **6**, 662) for specimens of abietic acid prepared by the Steele method from levopimaric acid.

‡ *Bull. Soc. chim.* 1926 [iv], **39**, 488; *Bull. Inst. Pin*, 1926, **22**, 349; see also *inter al.* Maly, *Annalen*, 1864, **129**, 96; Fremy and Sievert, *Zeit. für die gesammte Naturwiss.* 1849, **14**, 311; Aschan, *Annalen*, 1921, **424**, 117; Knecht and Hibbert, *J. Soc. Dyers and Colourists*, 1925, **41**, 329; Kesler, Lowy and Faragher, *J. Amer. C.S.* 1927, **49**, 2898.

§ *Chem. Ztg*, 1917, **41**, 666.

|| *J. pr. Chem.* 1910 [ii], **81**, 403.

¶ *Ibid.* 1912 [ii], **85**, 534.

* *J. Amer. C.S.* 1934, **56**, 1935.

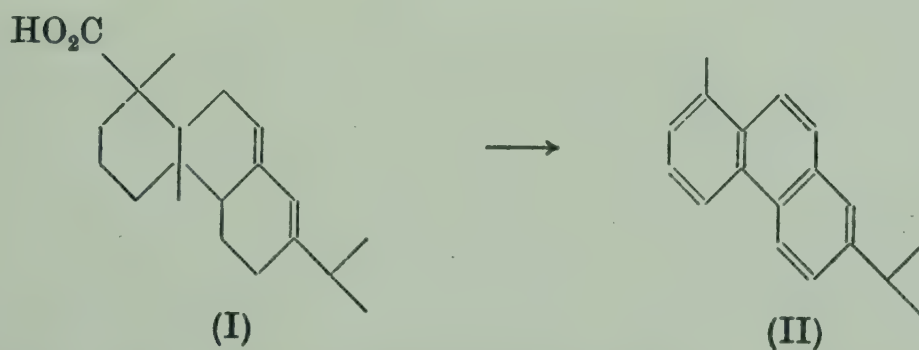
†† It may be pointed out here that the melting-points of abietic acid and levopimaric acid and their simple derivatives are never sharp, due to the partial isomerisation of the acids at their temperatures of fusion.

** Balas, *Casopis Cesk. Lekarnictva*, 1927, **7**, 320; Palkin and Harris, *loc. cit.*; Harris and Sanderson, *J. Amer. C.S.* 1948, **70**, 334; Lombard and Frey, *Bull. Soc. Chim.* 1948 [v], **15**, 1194.

Bardyshev* has described the preparation of an exceptionally pure abietic acid, m.p. 174–175°, $[\alpha]_D^{22} -115.6^\circ$ (in alcohol), by fractional crystallisation of the *dl-bornylamine salt*. A similar separation using the *fenchylamine salt* is also claimed.

As a result of a prolonged and difficult series of experiments abietic acid has been shown to have the formula (I); the principal evidence on which this is based is summarised below.

The main carbon skeleton of abietic acid was deduced from the important observation of Vesterberg† that the hydrocarbon retene, 1-methyl-7-isopropylphenanthrene, $C_{18}H_{18}$ (II), m.p. 100.5–101°, *picrate*, m.p. 124–125°, *styphnate*, m.p. 141–142°, *trinitrobenzoate*, m.p. 139–140°, was obtained on dehydrogenation with sulphur. The yield of retene is said to be greatly improved by the use of selenium‡ or palladised charcoal.§ Retene is also formed by the dehydrogenation of dihydroabietic acid and of tetrahydroabietic acid using palladised charcoal,|| which fact proves that retene is not an artefact formed by cyclisation during the reaction. Assuming that no unexpected rearrangement occurs during the dehydrogenation, the formation of retene from abietic acid accounts for 18 out of the original 20 carbon atoms. Decarboxylation is effected by loss of carbon dioxide and monoxide, and it was correctly concluded that the elimination of the second carbon atom must be due to its position as a quaternary methyl group.



The presence of three rings, and therefore of two double bonds, in abietic acid, as implied by the dehydrogenation experiments,

* *J. Gen. Chem. U.S.S.R.* 1941, **11**, 996; Krěstniskii and Bardyshev, *ibid.* 1940, **10**, 1894; compare Garkuscha, *ibid.* 1938, **8**, 1042, 1053.

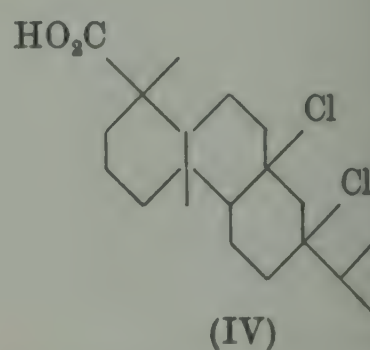
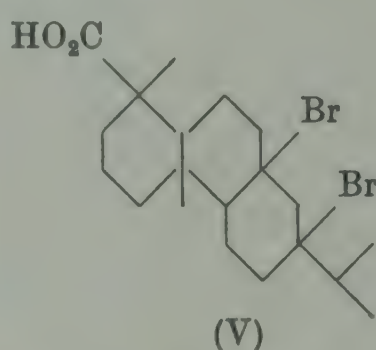
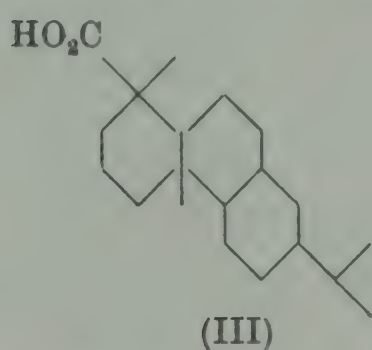
† *Ber.* 1903, **36**, 4200; compare Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 581; Madinareitia, *An. Soc. Españ. fís. y quim.* 1923, **20**, 237; Cheung, *Bull. Inst. Pin.*, 1929, p. 159; Nagel and Körnchen, *Chem. Umshau*, 1932, **39**, 1.

‡ Diels and Karstens, *Ber.* 1927, **60**, 2323.

§ Ruzicka and Waldmann, *Helv. Chim. Acta*, 1933, **16**, 842.

|| Ruzicka and Bacon, *Helv. Chim. Acta*, 1937, **20**, 1542.

has been confirmed by a very large body of evidence. By catalytic hydrogenation the acid can be reduced to the saturated acid, *tetrahydroabietic acid*, $C_{20}H_{34}O_2$ (III), m.p. ca. 182° , $[\alpha]_D$ ca. $+6^\circ$ (in alcohol), *methyl ester*, m.p. $44-45^\circ$,* which is also obtained as a by-product in the preparation of dehydroabietic acid (see p. 417).† Abietic acid forms a *dihydrochloride* (IV), m.p. 205° decomp.,‡ and a *dihydrobromide* (V), m.p. $175-176^\circ$ decomp., $[\alpha]_D \pm 0^\circ$ to $+29.2^\circ$ (in ethyl acetate).§ The iodine number of abietic acid is also said to indicate the presence of two double bonds.¶ Abietic acid can be titrated with per-acid, when it consumes two equivalents, the first rapidly and the second only slowly.¶ The presence of two double bonds implied by this experiment has been confirmed by per-acid titrations of specimens of dihydroabietic acid and its methyl ester (see p. 407), both of which consume only one equivalent per molecule.** Molecular refraction studies are also in agreement with the presence of two double bonds.††



* Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 315; Ruzicka and Schinz, *ibid.* 1923, **6**, 670; Vocke, *Annalen*, 1932, **497**, 247; Ruzicka and Kaufmann, *Helv. Chim. Acta*, 1941, **24**, 1389; compare Greth, *Zeit. Angew. Chem.* 1934, **47**, 827; Ruzicka et al., *Helv. Chim. Acta*, 1938, **21**, 591; Fleck and Palkin, *J. Amer. C.S.* 1938, **60**, 921.

† A tetrahydroabietic acid, m.p. 170° , $[\alpha]_D^{20} +47^\circ$, with somewhat different properties has been reported by Lombard (*Compt. rend.* 1939, **208**, 1321; *Bull. Soc. chim.* 1942 [v], **9**, 833) to be formed by high-pressure hydrogenation of abietic acid using a Raney nickel catalyst. Working in ethereal solution under pressure and using the same catalyst Lombard (*Bull. Soc. chim.* 1944 [v], **11**, 526) has claimed the preparation of a further *tetrahydroabietic acid*, m.p. 151° , $[\alpha]_D +17^\circ$ (in alcohol), *methyl ester*, m.p. 95° , $[\alpha]_D +18.5^\circ$ (in alcohol).

‡ Rau and Simonsen, *Ind. For. Rec.* 1925, **11**, 207; Levy, *Ber.* 1931, **64**, 2441; compare Hasselström and McPherson, *J. Amer. C.S.* 1939, **61**, 2247.

§ Levy, *Ber.* 1931, **64**, 2441; compare Koritschoner, *Zeit. Angew. Chem.* 1907, **20**, 641; Levy, *Zeit. Anorg. Chem.* 1913, **81**, 148; Ronin, *Bull. Inst. Pin*, 1928, pp. 167 and 173; Hasselström and McPherson, *J. Amer. C.S.* 1939, **61**, 1228.

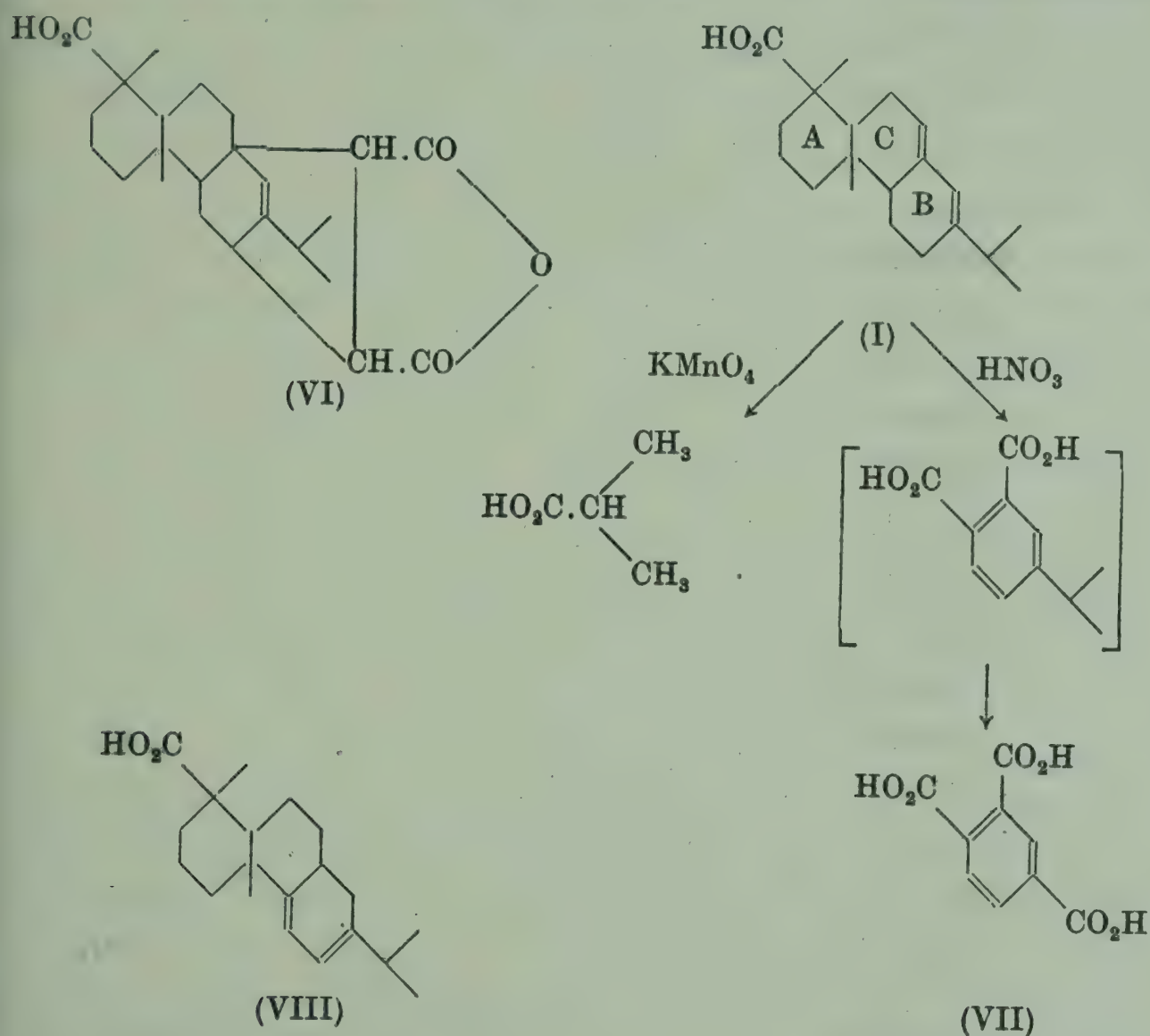
¶ Fahrion, *Zeit. Angew. Chem.* 1901, **14**, 1253; but see Johansson, *Arkiv. Kemi. Min. Geol.* 1917, **6**, No. 19.

¶ Ruzicka, Huyser and Seidel, *Rec. trav. chim.* 1928, **47**, 363; Kraft, *Annalen*, 1936, **524**, 1; Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, 1938, **21**, 591.

** Ruzicka, Huyser and Seidel, *loc. cit.*; Ruzicka, Bacon, Sternbach and Waldmann, *loc. cit.*

†† Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 315.

The two ethylenic linkages in abietic acid must be conjugated since it gives a red coloration with diazotised *p*-nitraniline,* and both the acid and its esters react with maleic anhydride to form the same adducts (for example VI) as are obtained from levo-pimaric acid and its esters (see p. 431).† These conjugated ethylenic linkages in abietic acid must, moreover, be distributed between two different rings, for the ultra-violet absorption spectrum shows a maximum at 240 m μ , $\log \epsilon = 4.15$ (in alcohol).‡



An important clue to the position of the double bonds was furnished at a fairly early date by the observations that *trimellitic acid* (VII) was produced by the oxidation of abietic acid or colophony with either nitric acid, manganese dioxide and

* Fieser and Campbell, *J. Amer. C.S.* 1938, **60**, 159.

† Ruzicka, Ankersmit and Frank, *Helv. Chim. Acta*, 1932, **15**, 1289; Arbusov, *J. Gen. Chem. U.S.S.R.* 1932, **2**, 806; compare Wienhaus and Sandermann, *Ber.* 1936, **69**, 2202; Ruzicka, Bacon, Lukes and Rose, *Helv. Chim. Acta*, 1938, **21**, 583.

‡ Sandermann, *Ber.* 1941, **74**, 154; compare Kraft, *Annalen*, 1935, **520**, 133; Wienhaus, Ritter and Sandermann, *Ber.* 1936, **69**, 2198; Ruzicka and Sternbach, *Helv. Chim. Acta*, 1938, **21**, 565; Fieser and Campbell, *loc. cit.*

sulphuric acid, or chromic acid.* Having regard to the formula for retene this oxidation product can only come from ring B of the abietic acid molecule, which most probably therefore contains at least one of the two double bonds. Additional evidence that the isopropyl group must be attached to the same carbon atom as one of the double bonds was provided by experiments showing that on vigorous oxidation of abietic acid with potassium permanganate some *isobutyric acid* could be isolated.† The evidence summarised above provides strong support for the view that the two ethylenic linkages of abietic acid must be in the positions shown in (I). Rigid proof of this is given later on p. 391 *et seq.*

The determination of the position of the carboxyl group in abietic acid afforded considerable difficulty. From its general reactions it had been suggested‡ that it was probably in a tertiary position, but this was difficult to reconcile with the following direct chemical evidence. When methyl abietate (see p. 406) was reduced by the Bouveault-Blanc method a primary alcohol, *abietinol*, $C_{20}H_{32}O$, b.p. $163-167^{\circ}/0.1$ mm., $d_4^{17^{\circ}} 1.0305$, $n_D^{17^{\circ}} 1.5487$, was obtained, yielding on catalytic hydrogenation *dihydro-abietinol*, b.p. $169-171^{\circ}/0.5$ mm. This alcohol was dehydrated by either phosphorus pentachloride or naphthalene- β -sulphonic acid to the triply unsaturated hydrocarbon, *methylabietin*, $C_{20}H_{30}$, b.p. $127-129^{\circ}/0.7$ mm., $d_4^{20^{\circ}} 0.964$, $d_4^{17^{\circ}} 0.9750$, $n_D^{20^{\circ}} 1.5311$, $n_D^{17^{\circ}} 1.5444$, $\alpha_D + 56.2^{\circ}$. On dehydrogenation with sulphur abietinol afforded retene; whilst on similar treatment with sulphur or selenium methylabietin gave a phenanthrene hydrocarbon, *homoretene*, $C_{19}H_{20}$, m.p. $81-82^{\circ}$.§ Since this homoretene fur-

* Shreder, *Annalen*, 1874, **172**, 98; Emmerling, *Ber.* 1879, **12**, 1441; Ruzicka, Schinz and Meyer, *Helv. Chim. Acta*, 1923, **6**, 1077; Ruzicka and Pfeiffer, *ibid.* 1925, **8**, 632; but see Virtanen, *Annalen*, 1921, **424**, 200; Levy, *Ber.* 1929, **62**, 2497.

† Levy, *Ber.* 1909, **42**, 4305; Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 637; Fieser and Campbell, *J. Amer. C.S.* 1938, **60**, 159; compare Emmerling, *Ber.* 1879, **12**, 1445; Dupont and Rouin, *Bull. Inst. Pin*, 1928, p. 203. (According to Schulz (*Coll. trav. chim. Tcheosl.* 1937, **9**, 542) 0.9 mole of oxalic acid is also formed per mole of abietic acid during vigorous potassium permanganate oxidation, but this observation and the derived deduction that abietic acid must be represented by (VIII) are of no significance in view of the great body of evidence that now supports (I).)

‡ Fahrion, *Zeit. Angew. Chem.* 1901, **14**, 1197; Levy, *Zeit. Anorg. Chem.* 1913, **81**, 147; compare Kailan and Antropp, *Monatsh.* 1929, **52**, 297; Shaefer and Piccard, *Ind. Eng. Chem., Anal. Ed.*, 1938, **10**, 515.

§ Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 581; Ruzicka and Jacobs, *Rec. trav. chim.* 1938, **57**, 509.

nished a *phenanthraquinone* derivative, m.p. 147° (*quinoxaline* derivative, m.p. 165°), on oxidation with chromic acid without loss of a methyl group, it was concluded that the carboxyl group of abietic acid must be secondary and occupy one of the positions 2, 3 or 4.

However, it was subsequently recognised * that this conclusion was incorrect and that the formation of methylabietin from abietinol involved a molecular rearrangement. Ruzicka, de Graaff and Müller found that on oxidation with potassium ferricyanide homoretene afforded *phenanthrene-1:7-dicarboxylic acid* (IX), whilst the phenanthraquinone prepared from homoretene (see above) gave by oxidation with potassium permanganate, *diphenyl-1:2:1':3'-tetracarboxylic acid* (X).

These unexpected results could only be explained if it was assumed that the methyl group situated at C_1 in abietic acid had been converted into an ethyl group in homoretene and that this hydrocarbon must therefore be *1-ethyl-7-isopropylphenanthrene* (VI). Confirmation of this view was provided by Haworth's synthesis of homoretene.†

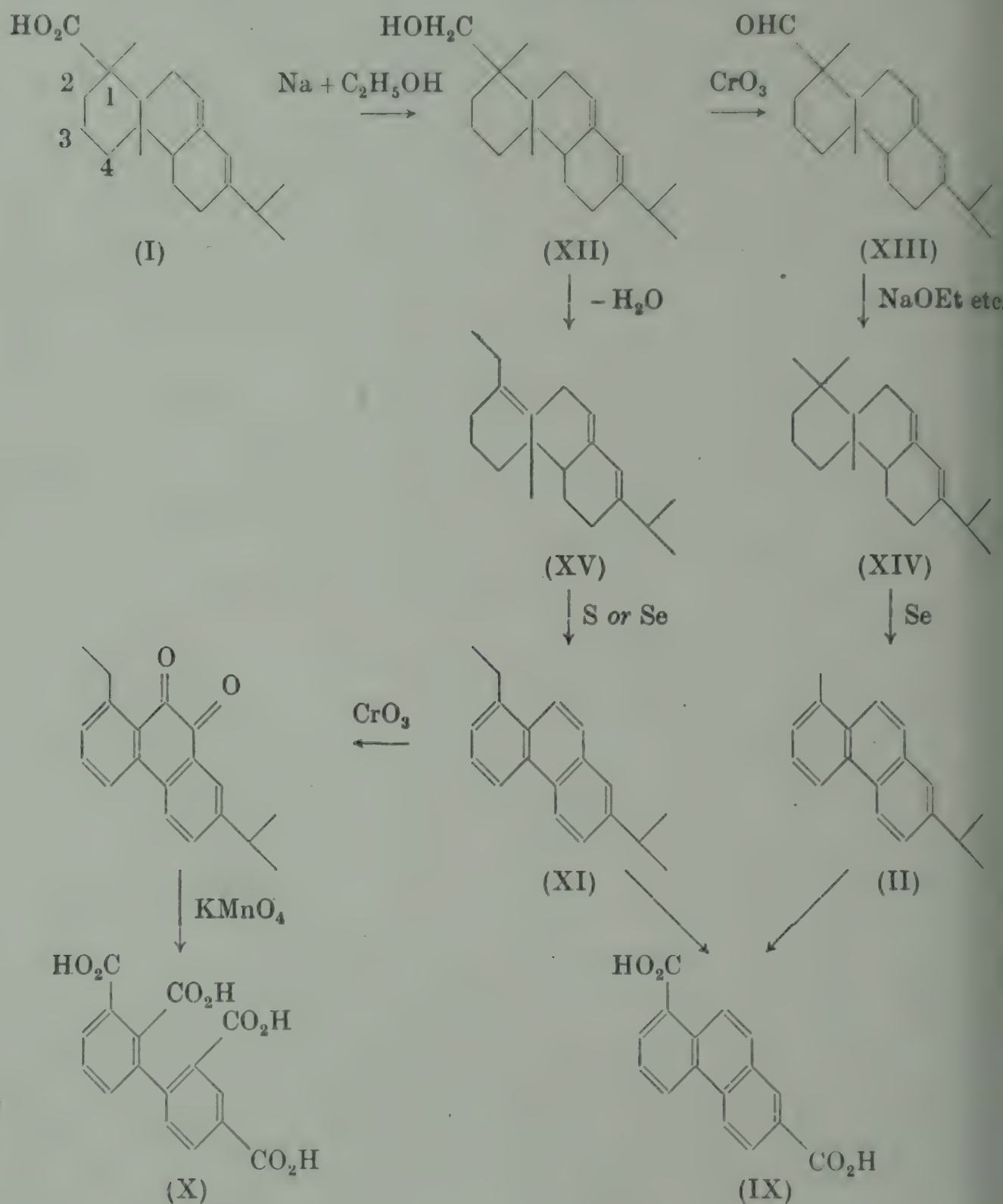
Since abietinol (XII) can be oxidised by chromic acid to *abietinal* (XIII), *semicarbazone*, m.p. 215° , which on reduction by the Wolff-Kishner method gave *methylabieten*, $C_{20}H_{32}$ (XIV), b.p. $135-138^{\circ}/0.15$ mm., $d_4^{24^{\circ}} 0.9734$, $n_D^{24^{\circ}} 1.5313$, dehydrogenated by selenium to retene, rearrangement must occur during the dehydration and methylabietin must most probably be represented by (XV).‡ Further confirmation of the position of the carboxyl group in abietic acid and a proof also of the positions of the quaternary methyl groups has been provided by the following evidence. By energetic oxidation with potassium permanganate and/or nitric acid or by vigorous ozonolysis two homologous *tricarboxylic acids*, $C_{11}H_{16}O_6$ (XVI), m.p. 219° (p. 390), *trimethyl ester* (XVIa), m.p. 75° and $C_{12}H_{18}O_6$ (XVII), m.p. $212-213^{\circ}$, *trimethyl ester* (XVIIa), b.p. $133-134^{\circ}/0.1$ mm., were obtained from abietic acid or its methyl ester.§ By dehydro-

* Vocke, *Annalen*, 1932, 497, 247; Ruzicka, de Graaff and Müller, *Helv. Chim. Acta*, 1932, 15, 1300; Haworth, *J.C.S.* 1932, p. 2717. † Haworth, *loc. cit.*

‡ Ruzicka, Waldmann, Meier and Hösli, *Helv. Chim. Acta*, 1932, 16, 169.

§ Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, 8, 637; Levy, *Ber.* 1929, 62, 2497; Ruzicka, Goldberg, Huyser and Seidel, *Helv. Chim. Acta*, 1931, 14, 545; compare Shreder, *Annalen*, 1874, 172, 96; Emmerling, *Ber.* 1879, 12, 1445; Levy, *Zeit. Anorg. Chem.* 1913, 81, 151; Aschan and Levy, *Ber.* 1927, 60, 1923.

genation with selenium the tricarboxylic acid (XVI) afforded *m*-xylene (XVIII), whilst its higher homologue (XVII) gave *hemimellitene* (1:2:3-trimethylbenzene) (XIX) with the same



reagent. This proves the 1:3 relationship of the two methyl groups in (XVI) and (XVII), as does the observation of Ruzicka and Waldmann,* that on vigorous oxidation of abietic acid with potassium permanganate some 1:3-dimethylcyclohexanone (XX

* *Helv. Chim. Acta*, 1933, 16, 842.

is formed. These observations provided an explanation for some earlier experiments which had been recorded by Vocke,* which had led him to suggest that the carboxyl group in abietic acid must be in a tertiary position. By the action of phenyl magnesium bromide on tetrahydroabietic acid he had obtained a *carbinol*, $C_{32}H_{44}O$ (XXI), which could not be smoothly oxidised by chromic acid. He found also that when the tricarboxylic acid (XVI) was heated with red phosphorus and bromine a mixture of the corresponding *anhydride*, $C_{11}H_{14}O_5$ (XXII), m.p. 170–172° and three *bromoanhydrides*, $C_{11}H_{13}O_5Br$ (XXIII), m.p. 215°, $C_{11}H_{12}O_4Br_2$ (XXIV), m.p. 207°, and $C_{11}H_{13}O_4Br$ (XXV), m.p. 160°, was formed. The formulae for these three bromo compounds are not certain and the anhydride bridge may be as in (XXII). By the action of sodium hydroxide on the two anhydrides (XXIII) and (XXIV) an unsaturated *dicarboxylic acid*, $C_{10}H_{14}O_4$, m.p. 183°, *methyl ester*, m.p. 132°, was obtained, which Vocke represented by (XXVI), since it gave on ozonolysis a keto-acid yielding on further oxidation with chromic acid α -*methylglutaric acid* (XXVII), whilst with aqueous sulphuric acid it was isomerised to a *lactone*, $C_{10}H_{14}O_4$ (XXVIII), m.p. 146°. Although at the time these experiments were carried out they were open to a different interpretation,[†] Rydon's synthesis of the acid (XXVI) and the lactone (XXVIII)[‡] has shown Vocke's interpretation of his results to be correct.

It can be deduced from the facts given above that the formula (I) correctly represents abietic acid and the most recent work has completely confirmed this formula. When abietic acid is oxidised with relatively small amounts of potassium permanganate under mild conditions a number of interesting and important products are formed. Mach[§] was the first to study such a reaction, but could only isolate ill-defined amorphous substances. Levy^{||} was more successful and prepared a crystalline α -*tetrahydroxyabietic acid*, $C_{20}H_{34}O_6$, m.p. 248–250°, in small yield by using redistilled

* *Loc. cit.*

† Compare Ruzicka, Waldmann, Meier and Hösli, *Helv. Chim. Acta*, 1932, **16**, 169.

‡ *J.C.S.* 1937, p. 257.

§ *Monatsh.* 1894, **15**, 627; compare Fahrion, *Zeit. Angew. Chem.* 1901, **14**, 1230.

|| *Ber.* 1909, **42**, 4305.

abietic acid.* Wienhaus[†] was only able to repeat Levy's results by using an abietic acid prepared by the hydrochloric acid method, but Levy[‡] subsequently showed that the formation of the α -tetrahydroxy-acid was a characteristic property of abietic acid. Ruzicka and Meyer,[§] who worked under similar conditions, did not obtain α -tetrahydroxyabietic acid, but instead a *dihydroxyabietic acid*, $C_{20}H_{32}O_4$, m.p. 153–154°, $[\alpha]_D^{20} - 29.7^\circ$ (in alcohol), giving two probably stereoisomeric *diacetates*, m.p.s 163° and 240°, and having one double bond as shown by per-acid titration.^{||}

In a series of brilliant investigations Ruzicka and Sternbach[¶] have made a thorough study of these oxidation products of abietic acid, which has proved in a most elegant and rigid manner the position of the double bonds at 7:8 and 14:9. The first product of the oxidation with potassium permanganate of abietic acid must be the dihydroxyabietic acid, $C_{20}H_{32}O_4$, *methyl ester*, m.p. 106–107°, now given the formula (XXIX), which then appears to be further attacked with formation of *oxidodihydroxyabietic acid*,** $C_{20}H_{32}O_5$ (XXX), m.p. ca. 130–150°, $[\alpha]_D - 52^\circ$ (in methanol). This oxide is unstable in aqueous media and is rapidly hydrated to γ -tetrahydroxyabietic acid, m.p. ca. 130–150°.

* It is desirable to point out here certain inconsistencies in nomenclature. Strictly speaking this acid should be called *tetrahydroxytetrahydroabietic acid* and similarly the related chlorotrihydroxyabietic acid should be called *chlorotrihydroxytetrahydroabietic acid*. Likewise dihydroxyabietic acid should be known as *dihydroxydihydroabietic acid*. There is already confusion in the literature with regard to dihydroxy-d-pimaric acid (see p. 451), which has been more correctly termed by some workers *dihydroxydihydro-d-pimaric acid*. Probably the most satisfactory nomenclature would be to regard all these abietic acid derivatives as springing from a hypothetical saturated parent hydrocarbon *abietane*, $C_{19}H_{34}$, when abietic acid itself would be $\Delta^{7:14(9)}$ -*abietadiene-1-carboxylic acid*, α -tetrahydroxyabietic acid would be *abietane-7, 8, 14, 9-tetraol-1-carboxylic acid*, levopimaric acid would be $\Delta^{6:8(14)}$ -*abietadiene-1-carboxylic acid* and so on.

[†] *Zeit. Angew. Chem.* 1921, **34**, 254.

[‡] *Ber.* 1926, **59**, 1302; 1929, **62**, 616, 2497; compare Aschan and Levy, *ibid.* 1927, **60**, 1923; Rouin, *Bull. Inst. Pin*, 1928, p. 197.

[§] *Helv. Chim. Acta*, 1923, **6**, 1097; compare Aschan, *Ber.* 1921, **54**, 867; Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 637.

^{||} Ruzicka and Sternbach, *Helv. Chim. Acta*, 1938, **21**, 565.

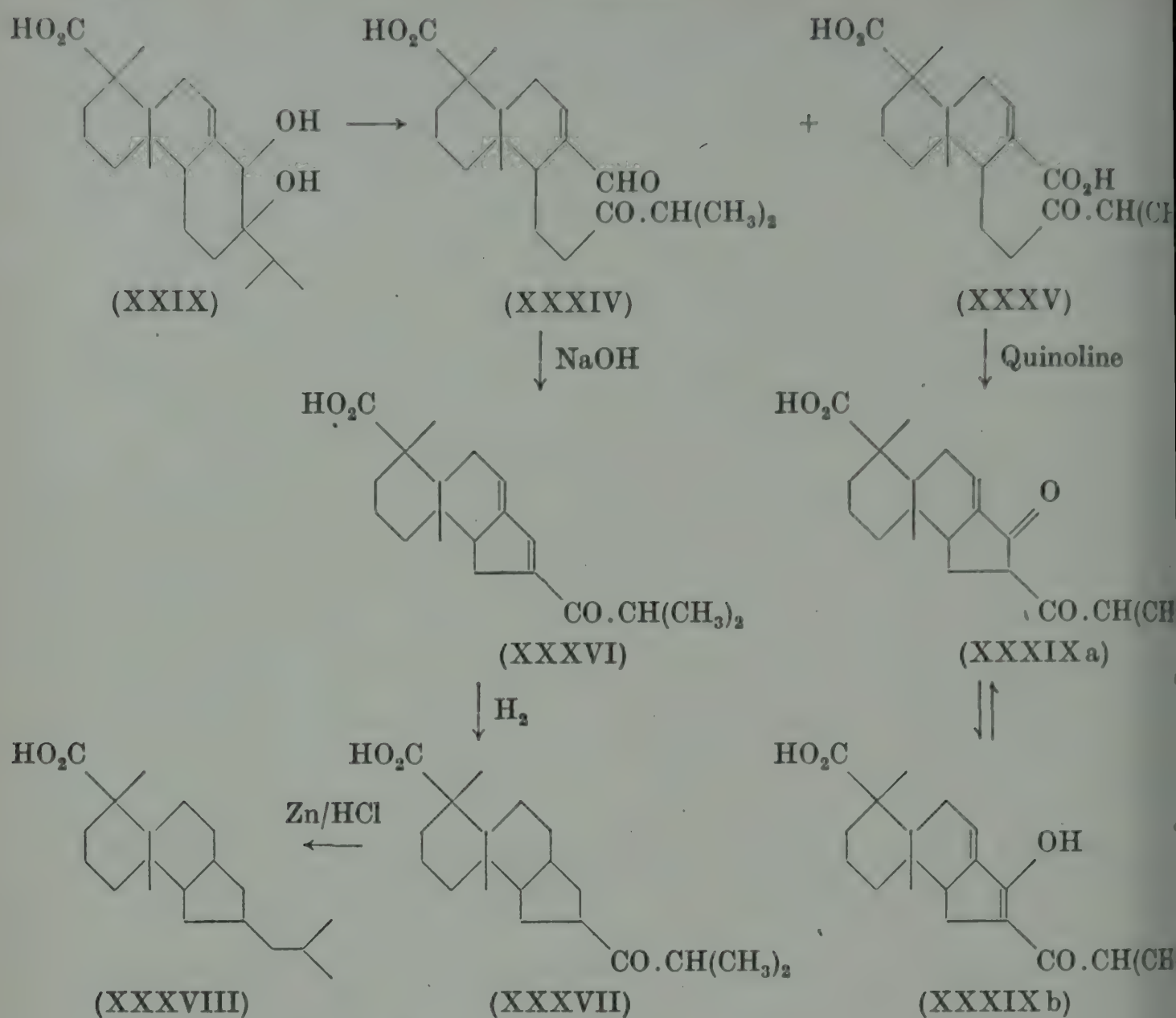
[¶] *Helv. Chim. Acta*, 1938, **21**, 565; 1940, **23**, 333, 341, 355; 1941, **24**, 492; 1942, **25**, 1036; Sternbach, *Rocz. Chem.* 1939, **19**, 167; Ruzicka, Sternbach and Jeger, *Helv. Chim. Acta*, 1941, **24**, 504.

** The direct isolation of this substance was only effected on one occasion, but it can be obtained by other methods as described later and its reactions make it appear very probable that it is an intermediate in the oxidation at this stage.

a slow mutarotation in neutral aqueous media to afford β -*tetrahydroxyabietic acid*, m.p. ca. 130–150°, $[\alpha]_D - 67^\circ$ (in methanol), *methyl ester*, m.p. 70–100°. On refluxing with dilute sulphuric acid in acetone solution both the β - and γ -acids were rearranged to the α -isomer and, whilst both the α - and β -acids were not affected by dilute hydrochloric acid, the γ -acid furnished a mixture of chlorotrihydroxyabietic acid and α -tetrahydroxyabietic acid with this reagent. γ -Tetrahydroxyabietic acid was, however, fairly stable towards cold, dilute sulphuric acid.

It appears, therefore, that the usual product isolated from the potassium permanganate oxidation of abietic acid under mild conditions is a mixture of dihydroxyabietic acid and γ -tetrahydroxyabietic acid, and that Levy's α -tetrahydroxyabietic acid is an artefact formed during the working up of the mixture. Both the β - and γ -tetrahydroxyabietic acids must be regarded merely as stereoisomers of the α -acid and therefore must also be represented by (XXXII). When the chlorotrihydroxy-acid (XXXI) was treated with dilute sodium hydroxide it afforded a mixture of oxidodihydroxyabietic acid (XXX) and γ -tetrahydroxyabietic acid. By dehydrogenation with selenium or palladised charcoal, dihydroxyabietic acid (XXIX), chlorotrihydroxyabietic acid (XXXI), α -tetrahydroxyabietic acid (XXXII), and oxidodihydroxyabietic acid (XXX), all afforded 7-hydroxy-1-methyl-phenanthrene (XXXIII), m.p. 190–191°, *acetate*, m.p. 137–138°, and doubtless retene, although the presence of this hydrocarbon was only proved in the case of the dehydrogenation of dihydroxyabietic acid. These dehydrogenations place with certainty one of the hydroxyls in all these compounds at the 7 position and thus confirm the relative position of the *isopropyl* group and one of the ethylenic linkages in abietic acid.

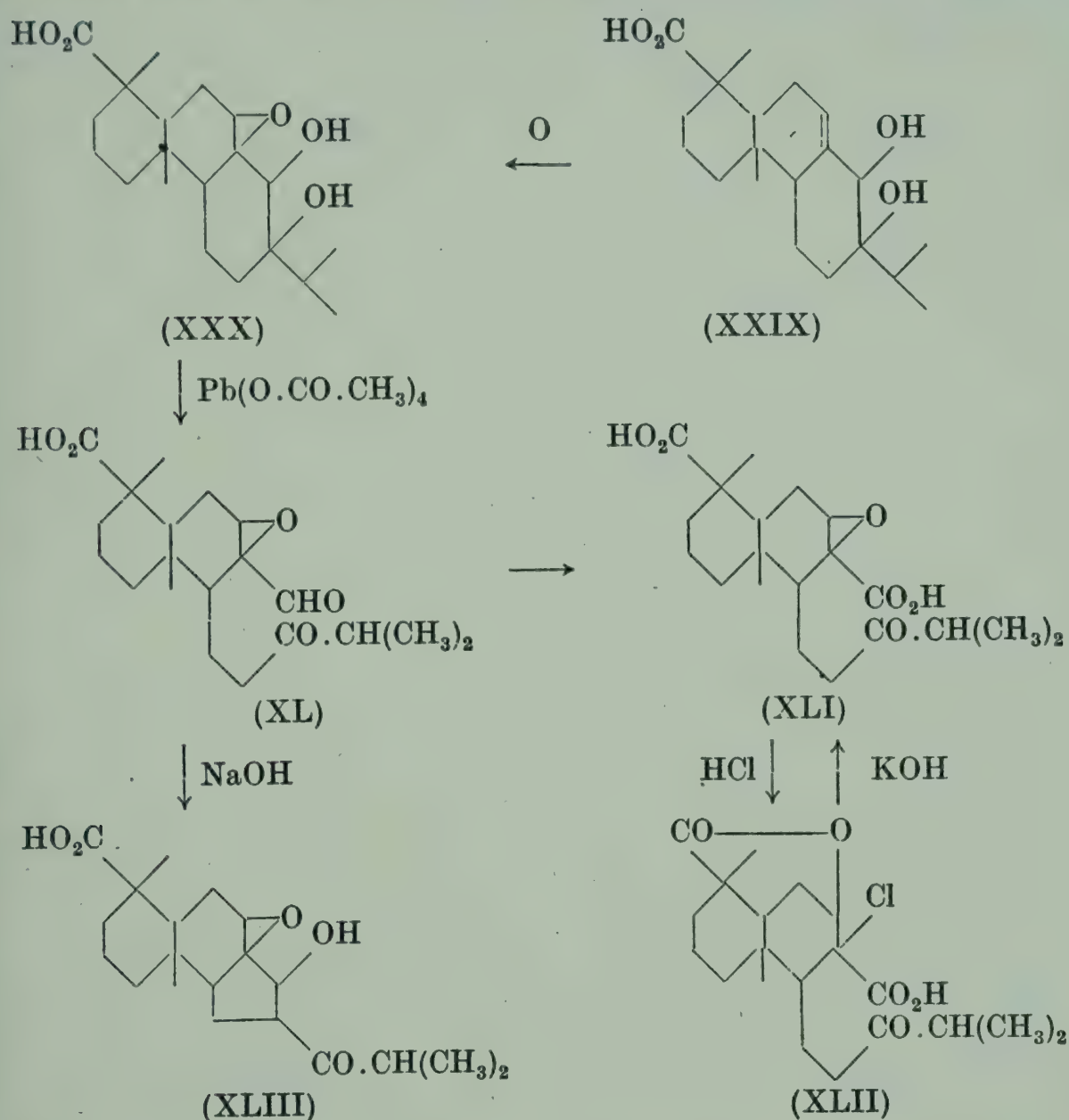
When dihydroxyabietic acid (XXIX) was treated with lead tetracetate it gave a mixture of an amorphous *aldehydo-keto-acid*, $C_{20}H_{30}O_4$ (XXXIV), *dioxime*, m.p. 188.5–189.5°, and the corresponding *keto-dicarboxylic acid*, $C_{20}H_{30}O_5$ (XXXV), m.p. 212–212.5°, *oxime*, m.p. 227–229°, having the absorption spectrum expected for an $\alpha:\beta$ -unsaturated acid. The latter compound (XXXV) was also formed by autoxidation of (XXXIV). On treatment with sodium hydroxide (XXXIV) underwent internal condensation with elimination of water to furnish the dienoid



ketonic acid, $\text{C}_{20}\text{H}_{28}\text{O}_3$ (XXXVI), m.p. $188-189^\circ$, λ max. ca. $305\text{ m}\mu$ with $\log \epsilon = 4.2$, oxime, m.p. 235° decomp., reduced by catalytic hydrogenation to a dihydro-derivative, $\text{C}_{20}\text{H}_{30}\text{O}_3$, m.p. $197-198^\circ$, or to a saturated ketonic acid, $\text{C}_{20}\text{H}_{32}\text{O}_3$ (XXXVII), oxime, m.p. $215-216^\circ$, semicarbazone, m.p. $219-220^\circ$. On reduction by Clemmensen's method the ketonic acid (XXXVII) afforded the saturated acid (XXXVIII), $\text{C}_{20}\text{H}_{34}\text{O}_2$, characterised as the methyl ester, b.p. $150-160^\circ/0.1\text{ mm}$. By heating with quinoline the keto-dicarboxylic acid (XXXV) underwent an internal dehydrational condensation to furnish a substance, $\text{C}_{20}\text{H}_{28}\text{O}_4$, m.p. 176° , λ max. $330\text{ m}\mu$ with $\log \epsilon = 4.2$, best regarded as a tautomeric mixture of (XXXIXa) and (XXXIXb).

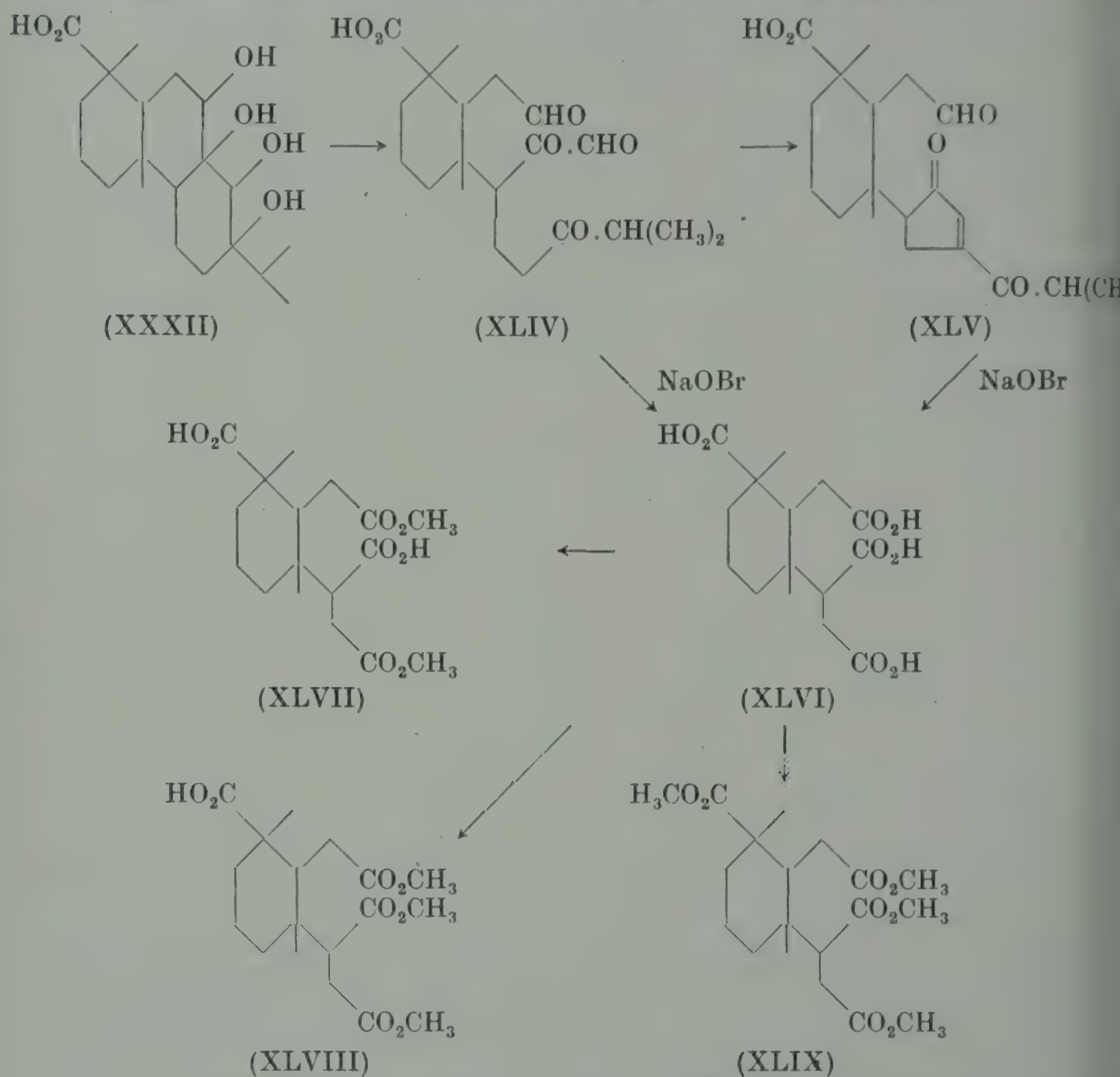
When dihydroxyabietic acid (XXIX) was treated with per-phthalic acid it afforded a crude oxidodihydroxyabietic acid which may have been identical with that previously described (p. 391) and which should likewise be represented by (XXX).

As would be expected it gave α -tetrahydroxyabiatic acid on boiling with dilute sulphuric acid in acetone solution. Both this oxide and that obtained, as mentioned previously, from chlorotrihydroxyabiatic acid furnished an *oxido-aldehydo-ketonic acid*,



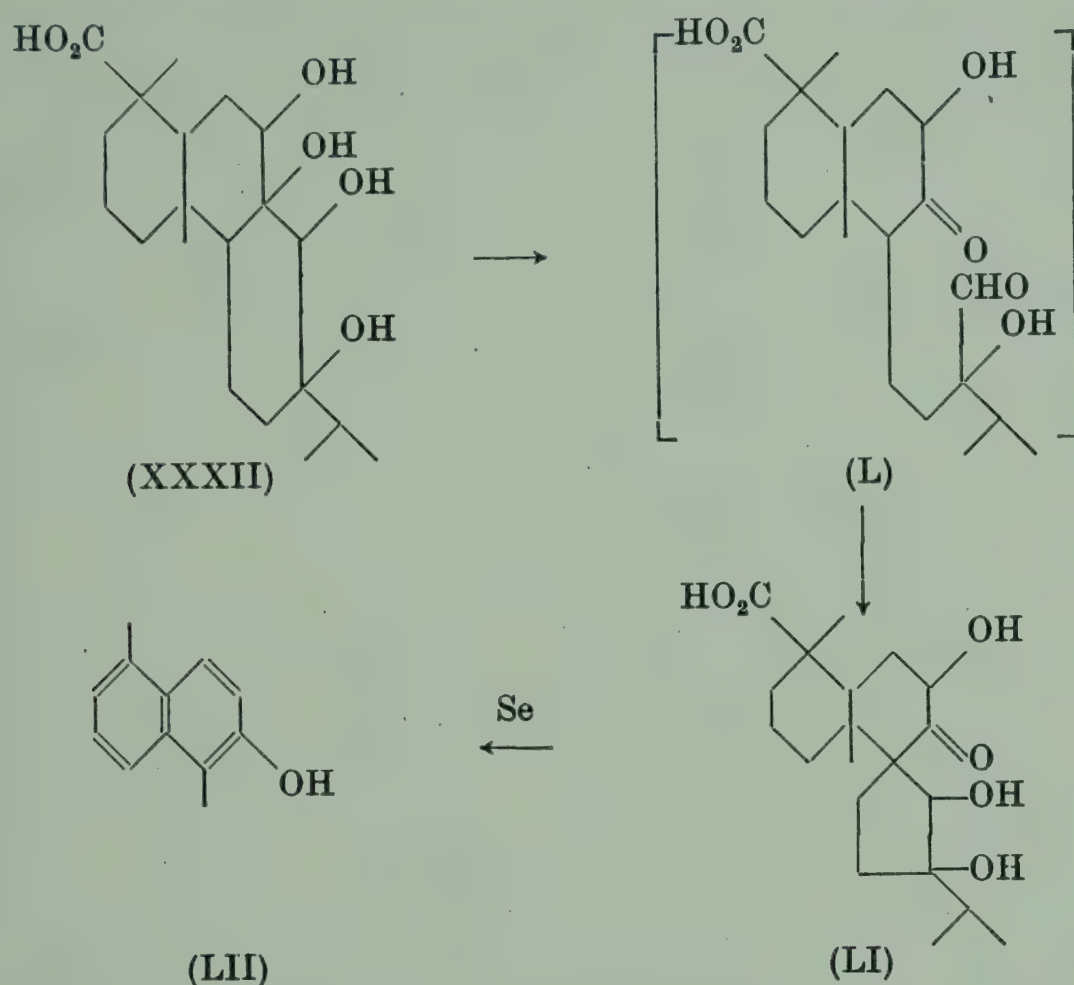
$\text{C}_{20}\text{H}_{30}\text{O}_5$ (XL), m.p. $132-134^\circ$, *dioxime*, m.p. $195.5-197^\circ$, on oxidation with lead tetra-acetate. Further oxidation of the acid (XL) with perphthalic acid afforded the corresponding *dicarboxylic acid*, $\text{C}_{20}\text{H}_{30}\text{O}_6$ (XLI), m.p. $156-158^\circ$, which was converted by hydrochloric acid to a *chlorolactonic acid*, $\text{C}_{20}\text{H}_{29}\text{O}_5\text{Cl}$, formulated as (XLII), m.p. $117-121^\circ$, from which it could be regenerated by treatment with alcoholic potassium hydroxide. Dilute sulphuric acid isomerised the acid (XLI) to a *substance*, $\text{C}_{20}\text{H}_{30}\text{O}_6$, m.p. $184.5-185^\circ$, for which no formula has as yet been suggested. By digestion with sodium hydroxide solution the aldehydo-acid (XL) underwent internal condensation to an

isomeric *hydroxyoxidoketonic acid* (probably (XLIII)), $C_{20}H_{30}O_5$, m.p. $190-192.5^\circ$, which by treatment with perphthalic acid gave a *compound*, $C_{20}H_{32}O_7$, m.p. $171-172^\circ$, of uncertain constitution. These experiments with dihydroxyabiatic acid prove that the more easily oxidised of the two ethylenic linkages present in abiatic acid must occupy the 7:8 position.



The oxidation of α -tetrahydroxyabiatic acid (XXXII) by lead tetra-acetate has also been studied by Ruzicka and Sternbach. The main product of the reaction was an indefinite *substance*, $C_{20}H_{28}O_5$ or $C_{20}H_{30}O_6$, *disemicarbazone*, m.p.s between 178° and 192° , *methyl ester*, b.p. $199-202^\circ/0.35$ mm. (*disemicarbazone*, m.p. *ca.* $170-180^\circ$ decomp.), which was probably a mixture of (XLIV) and (XLV), for on further oxidation with sodium hypobromite

it was smoothly degraded to a *tetracarboxylic acid*, $C_{15}H_{22}O_8$ (XLVI), m.p. $245-246.5^\circ$, $[\alpha]_D^{20}$ ca. -6° (in alcohol). In agreement with the formulation (XLVI), this tetracarboxylic acid gave a *dimethyl ester* (XLVII), m.p. $160-160.5^\circ$, with cold methanolic hydrogen chloride, a *trimethyl ester* (XLVIII), m.p. $104-106^\circ$, with the same reagent in the hot, and a *tetramethyl ester* (XLIX), m.p. $73.5-74.5^\circ$, with diazomethane.



A by-product in the lead tetra-acetate oxidation of α -tetrahydroxyabietic acid (XXXII) was a *substance*, $C_{20}H_{32}O_6$, m.p. $204-205^\circ$, $[\alpha]_D + 7^\circ$ (sodium salt in aqueous solution), which is probably identical with a so-called *tetrahydroxyabietic acid*, m.p. $208-210^\circ$, $[\alpha]_D \pm 0^\circ$ (in alcohol) obtained, in addition to the usual α -tetrahydroxyabietic acid, by Levy* in the potassium permanganate oxidation of abietic acid. Periodic acid and chromic acid can also be used in the preparation of this acid, but the yield is largely dependent upon how drastic is the treatment with mineral acid or alkali involved in working up the reaction mixture. This is probably due to the first stage in the oxidation of α -tetrahydroxyabietic acid being the formation of

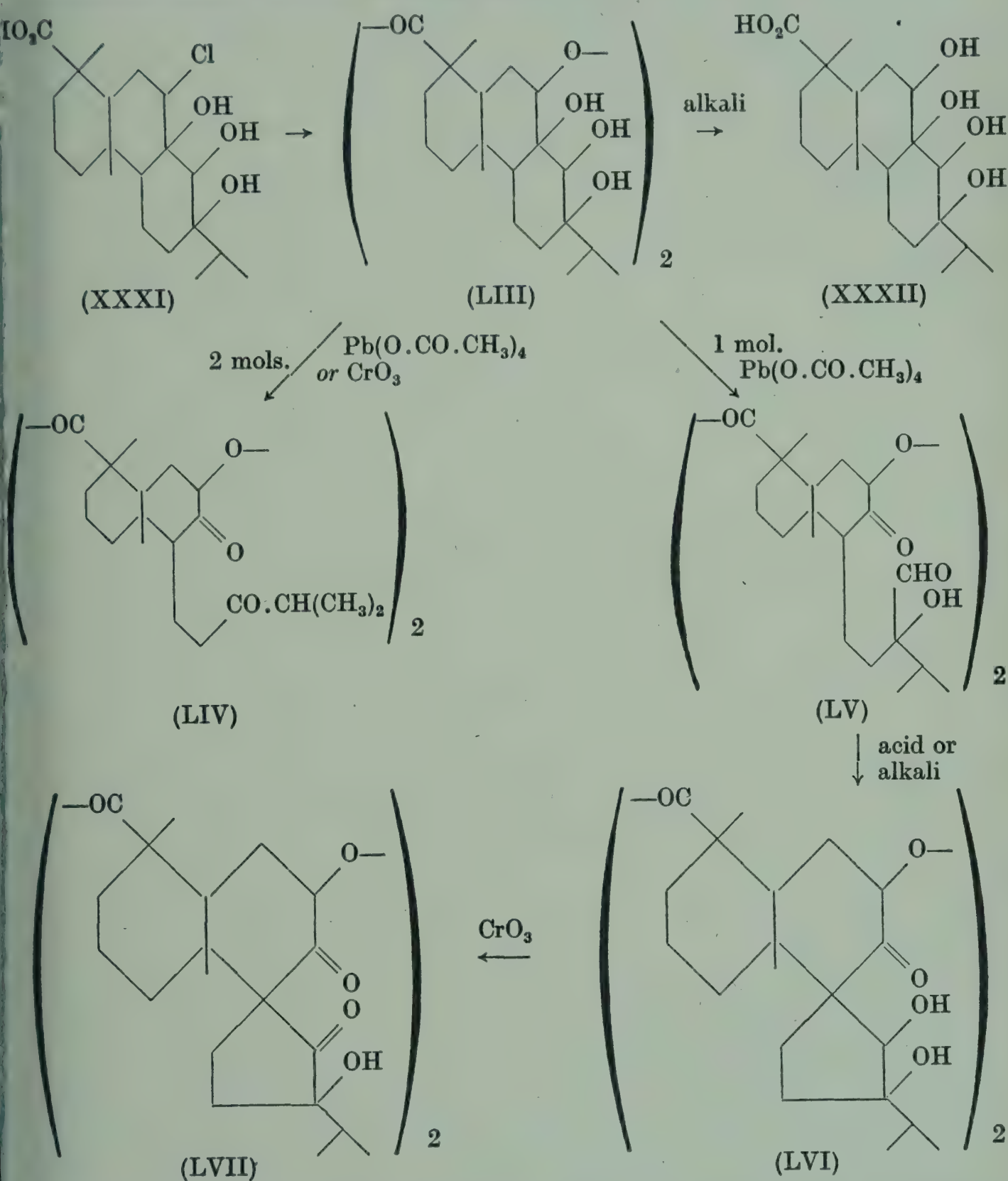
* Ber. 1926, 59, 1302.

a *keto-aldehydic acid* (L), which undergoes internal condensation to the substance, $C_{20}H_{32}O_6$, m.p. 204–205°, referred to above and which, therefore, may be represented by (LI). In agreement with this view Ruzicka and Sternbach found that it afforded, on dehydrogenation with selenium, a mixture of 1:5-*dimethyl 6-naphthol* (LII), m.p. 162–163°, *benzoate*, m.p. 151–151.5°, and a second, as yet unidentified, *dimethylnaphthol*, m.p. 99–100°.

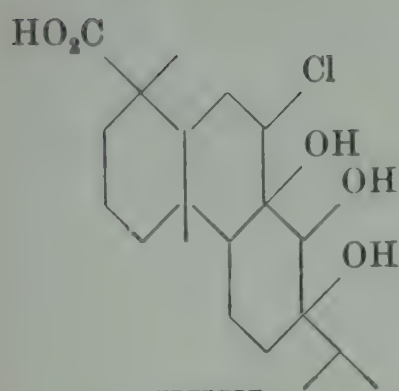
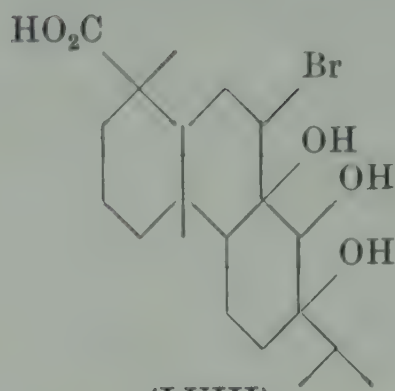
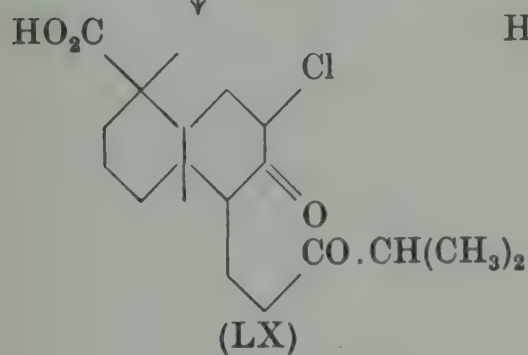
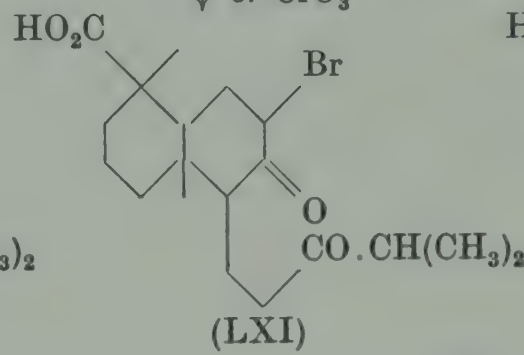
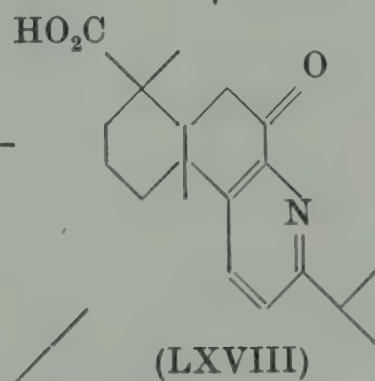
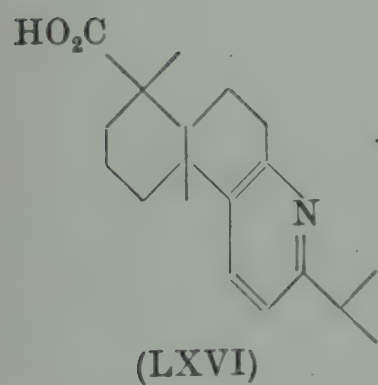
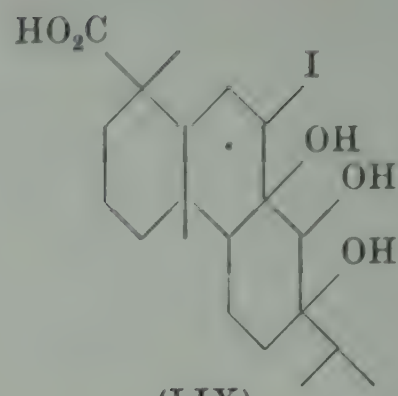
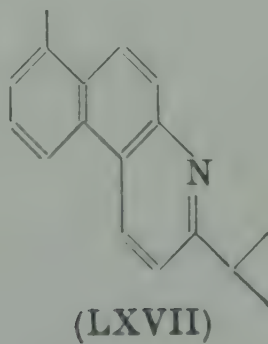
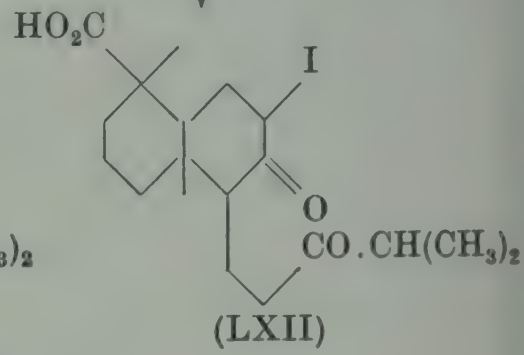
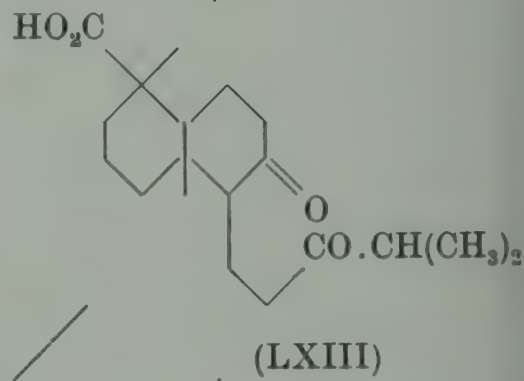
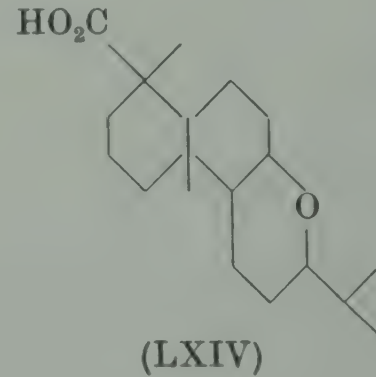
By boiling in toluene solution chlorotrihydroxyabietic acid (XXXI) was converted to a dimeric *tetrahydroxyabietinolactone*, $C_{40}H_{64}O_{10}$ (LIII), m.p. above 330°, $[\alpha]_D -77^\circ$ (in chloroform), *diacetate*, m.p. ca. 290°, which furnished α -tetrahydroxyabietic acid by alkaline hydrolysis, but only under very drastic conditions. The same lactone (LIII), together with β -tetrahydroxyabietic acid, was formed when the oxidodihydroxyabietic acid (XXX) (p. 394), obtained by the action of perphthalic acid on dihydroxyabietic acid, was allowed to stand in aqueous acetone solution. When this lactone was oxidised with two molecular proportions of lead tetra-acetate, or with chromic acid, a dimeric *diketolactone*, $C_{38}H_{56}O_8$ (LIV), m.p. 162–164° was formed, which gave only a *di-p-nitrophenylhydrazone*, m.p. 275–277°, the ketonic groups at the 14 position being hindered sterically. Oxidation of the lactone (LIII) with only one molecular proportion of lead tetra-acetate furnished an amorphous reaction product, doubtless (LV), which was isomerised to the crystalline dimeric *keto-lactone*, $C_{40}H_{60}O_{10}$ (LVI), m.p. ca. 300°, by digestion with acid or alkaline condensing agents. Further oxidation of (LVI) with chromic acid afforded the dimeric *diketo-lactone* (LVII), $C_{40}H_{56}O_{10}$, m.p. ca. 290–291°.

When abietic acid was oxidised with potassium permanganate and the resultant γ -tetrahydroxyabietic acid was treated with hydrobromic acid it gave the expected *bromotrihydroxyabietic acid*, $C_{20}H_{33}O_5Br$ (LVIII), m.p. 148–149°, (p. 400) whilst if hydriodic acid was used then the corresponding *iodotrihydroxyabietic acid*, $C_{20}H_{33}O_5I$ (LIX), m.p. ca. 120° decomp., was formed. By oxidation with two molecular proportions of lead tetra-acetate, chlorotrihydroxyabietic acid (XXXI) gave the *chlorodiketo-acid* (LX), $C_{19}H_{29}O_4Cl$, m.p. 157–158°, *monosemicarbazone*, m.p. 204–206°, whilst bromotrihydroxyabietic acid in exactly the same way, or by oxidation with chromic acid, afforded the corre-

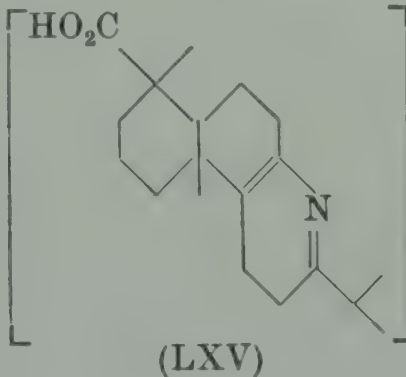
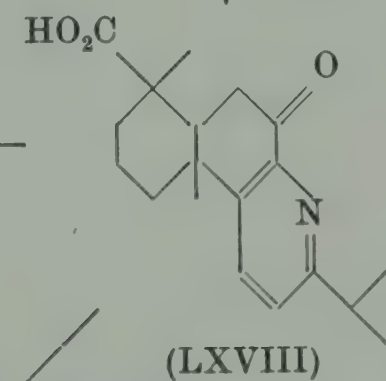
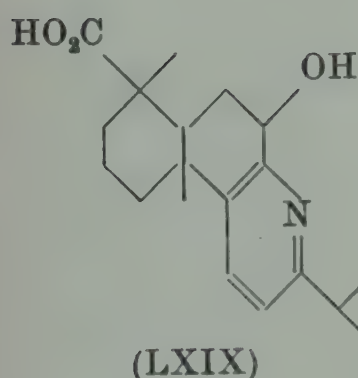
sponding *bromodiketo-acid*, $C_{19}H_{29}O_4Br$ (LXI), m.p. 138–145°. Iodotrihydroxyabietic acid behaved similarly, furnishing the *iododiketo-acid* (LXII), $C_{19}H_{29}O_4I$, m.p. 117–119° decomp., from



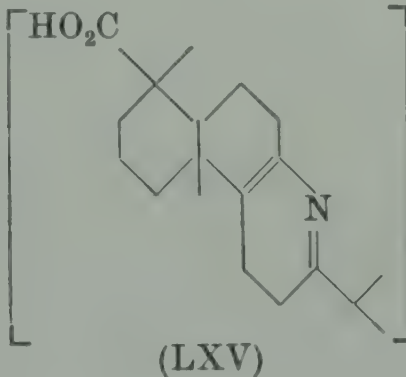
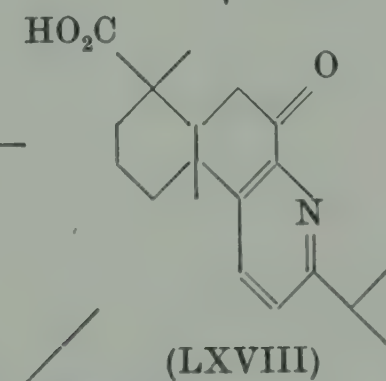
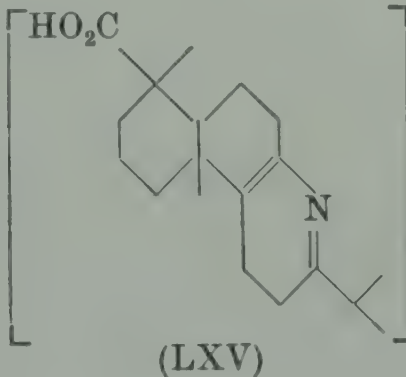
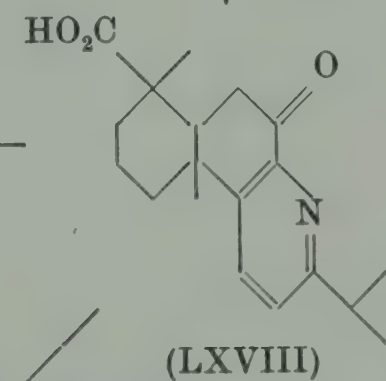
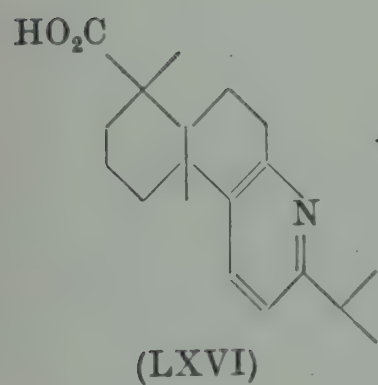
which by treatment with hydriodic acid the *diketo-acid* (LXIII), $C_{19}H_{30}O_4$, m.p. 123–124°, *monophenylhydrazone*, m.p. 191–192°, was obtained. This diketo-acid furnished a saturated *oxide*, $C_{19}H_{32}O_3$ (LXIV), m.p. 142–147°, on catalytic hydrogenation, whilst by treatment with ammonia it gave, presumably *via* the

2 moles. \downarrow $\text{Pb}(\text{O} \cdot \text{CO} \cdot \text{CH}_3)_4$ 2 moles. \downarrow $\text{Pb}(\text{O} \cdot \text{CO} \cdot \text{CH}_3)_4$
or CrO_3  \downarrow NH_3  \swarrow N_2H_4 /alkali etc. \searrow Se2 moles. \downarrow $\text{Pb}(\text{O} \cdot \text{CO} \cdot \text{CH}_3)_4$  \downarrow HI \swarrow NH_3 

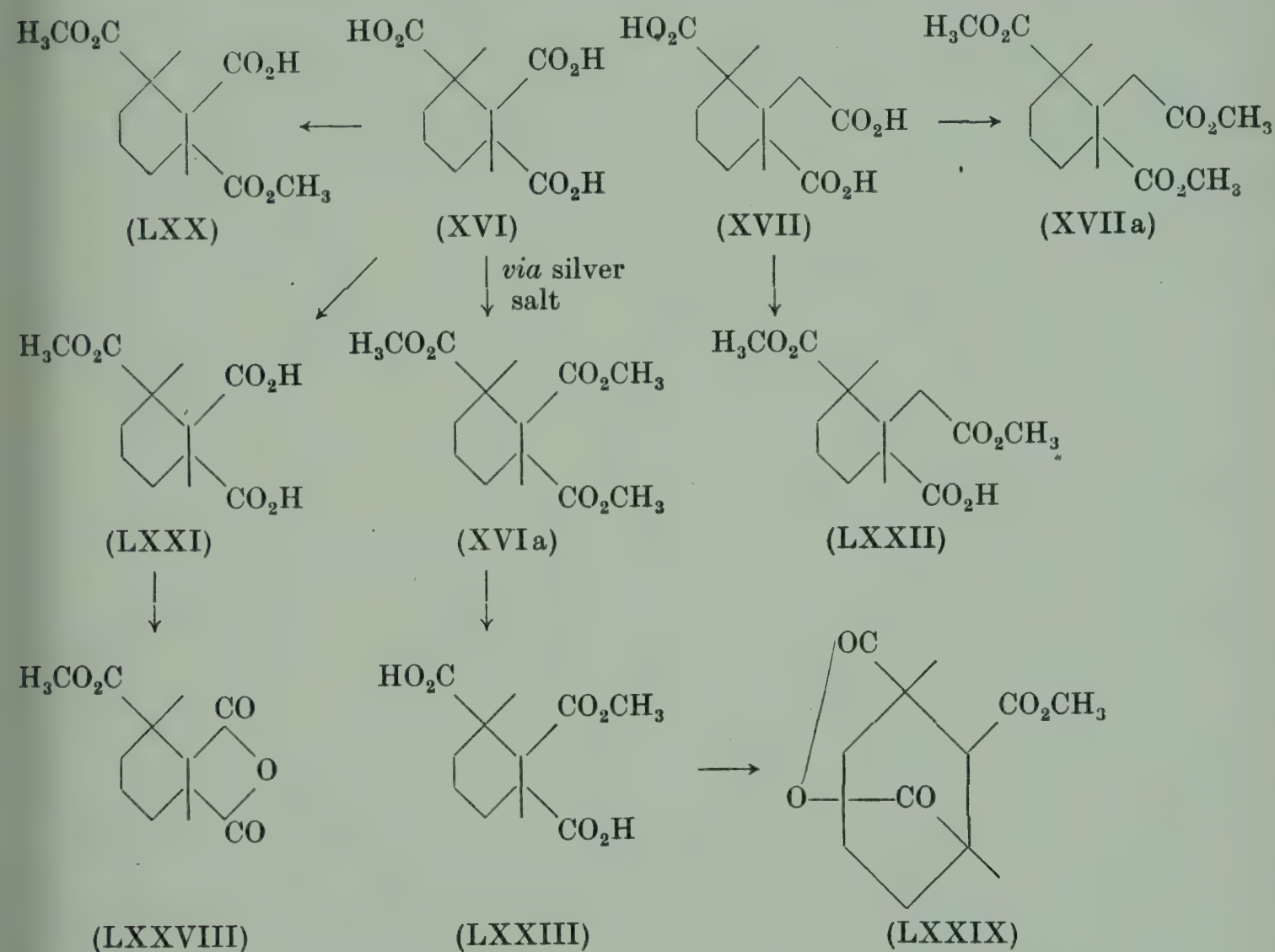
(LXIX)



(LXVI)



dihydropyridine (LXV), followed by disproportionation, 8-*azadehydroabietic acid*, $C_{19}H_{27}O_2N$ (LXVI), m.p. 258–260°, *picrate*, m.p. 221–223°, dehydrogenated by selenium to 8-*azaretene* (LXVII), m.p. 117.5–118.5°, *picrate*, m.p. 190–195° decomp., *trinitrobenzoate*, m.p. 100–101°, the identity of which was confirmed by its synthesis. The bromo- and iodo-diketo-acids,



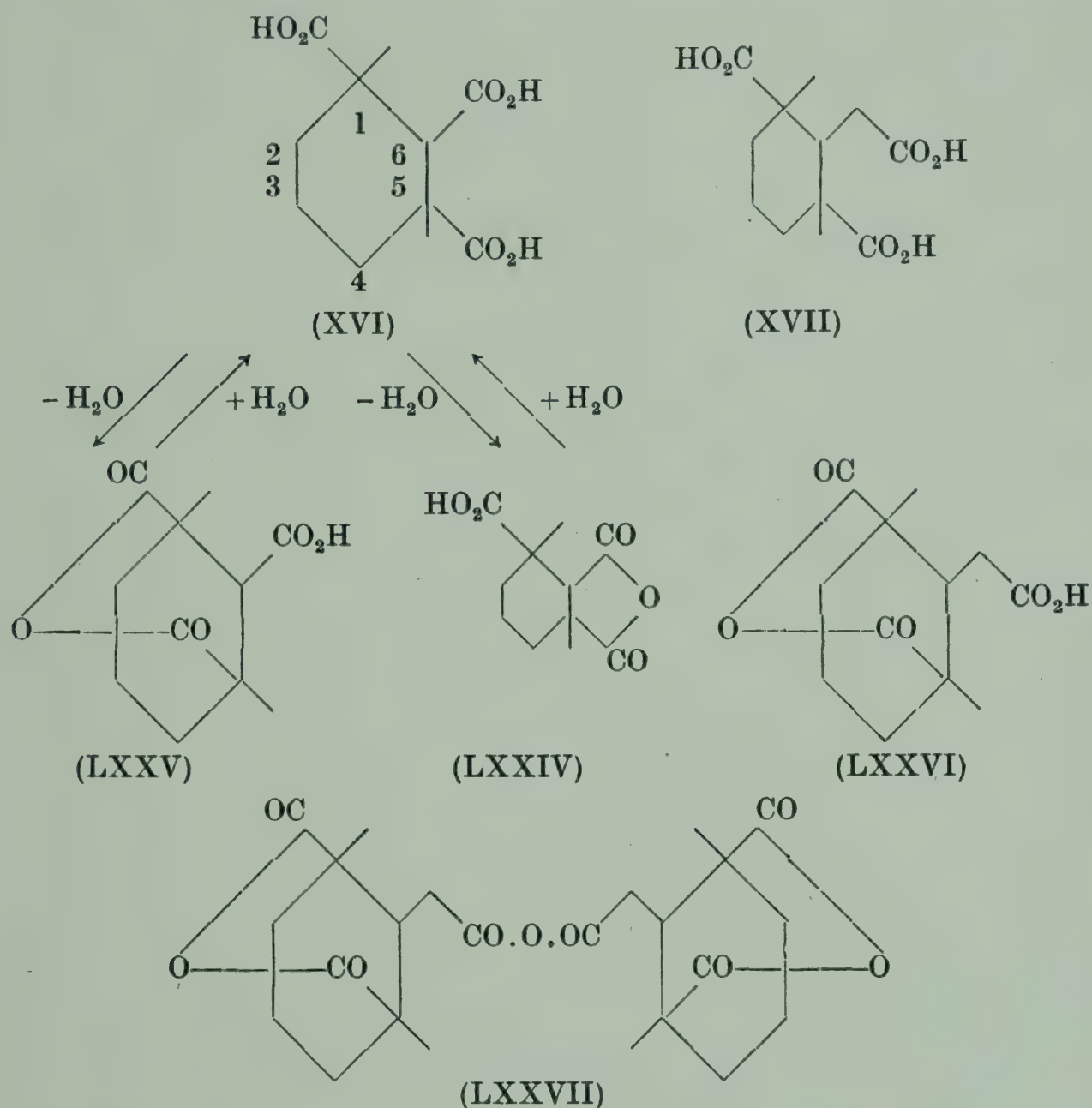
(LXI) and (LXII), underwent an unusual reaction when treated with ammonia, giving 9-*keto*-8-*azadehydroabietic acid*, $C_{19}H_{27}O_2N$ (LXVIII), m.p. 284–287°, *picrate*, m.p. 190–192°, which was catalytically hydrogenated to the corresponding 9-*hydroxy*-8-*azadehydroabietic acid*, $C_{19}H_{27}O_3N$ (LXIX), m.p. 205–206°, and which afforded 8-*azadehydroabietic acid* (LXVI) on reduction by the Wolff-Kishner method. This last series of experiments proved in a particularly elegant manner the correctness of the double bond positions in the now accepted abietic acid formula.

Ruzicka, Goldberg, Huyser and Seidel* were able to draw

* *Helv. Chim. Acta*, 1931, 14 545.

interesting conclusions regarding the stereostructure of abietic acid and the related resin acids from a study of the two homologous tricarboxylic acids, $C_{11}H_{16}O_6$ (XVI) and $C_{12}H_{18}O_6$ (XVII) (see p. 401). Depending upon the experimental conditions the acid $C_{11}H_{16}O_6$ was converted to either a *dimethyl ester*, $C_{13}H_{20}O_6$ (LXX), m.p. 119–120°, or a *monomethyl ester*, $C_{12}H_{18}O_6$ (LXXI), m.p. 154–156°. In the same way the acid $C_{12}H_{18}O_6$ afforded either the trimethyl ester (XVIIa), mentioned on p. 387, or a *dimethyl ester*, $C_{14}H_{22}O_6$ (LXXII), m.p. 148–149°. By alkaline hydrolysis the trimethyl ester (XVIIa), of the acid $C_{11}H_{16}O_6$, prepared by the silver salt method (see p. 387), gave a *monomethyl ester*, $C_{12}H_{18}O_6$ (LXXIII), m.p. 188–190°, differing from that (LXXI) prepared by direct esterification. By treatment with acetyl chloride the acid, $C_{11}H_{16}O_6$, was converted into a mixture of two *anhydrides*, $C_{11}H_{14}O_5$, m.p.s *ca.* 100° (probably (LXXIV)) and 170–172° (probably (LXXV), previously given the same formula designated (XXII) on p. 390), whilst the acid $C_{12}H_{18}O_6$ afforded similarly a mixture of an *anhydride*, $C_{12}H_{16}O_5$ (probably (LXXVI)), m.p. 182–183° and dimeric triple *anhydride*, $C_{24}H_{30}O_9$ (probably (LXXVII)), m.p. *ca.* 230°. By boiling with water the anhydrides (LXXIV), (LXXV) and (LXXVI) were smoothly reconverted to the parent acids, but the dimeric anhydride (LXXVII), being hindered sterically, required boiling aqueous hydrochloric acid to effect this reversion. With acetyl chloride the monomethyl ester (LXXI) of the acid $C_{11}H_{16}O_6$ gave an *anhydride*, $C_{12}H_{16}O_5$ (LXXVIII), m.p. 103–104°, whilst the isomeric monomethyl ester (LXXIII) afforded an *anhydride* (LXXIX), m.p. 137–137.5°. These experiments show that one of the carboxyl groups of the acid $C_{11}H_{16}O_6$ is very considerably hindered sterically and, as the acid $C_{12}H_{18}O_6$ is not affected in this way, the carboxyl concerned must be that at the 6 position as indicated in the above formulae. This view was supported by the observation that on electrolysis of the sodium salt of the dimethyl ester (LXX) of the acid $C_{11}H_{16}O_6$ by Kolbe's method a considerable amount of a bimolecular *ester* resulted, presumably (LXXX) (p. 404), which was not isolated in a state of purity, together with an unsaturated *ester*, presumably (LXXXI), which afforded on hydrolysis an unsaturated *dicarboxylic acid*, $C_{10}H_{14}O_4$, presumably (LXXXII), m.p. 163° decomp.

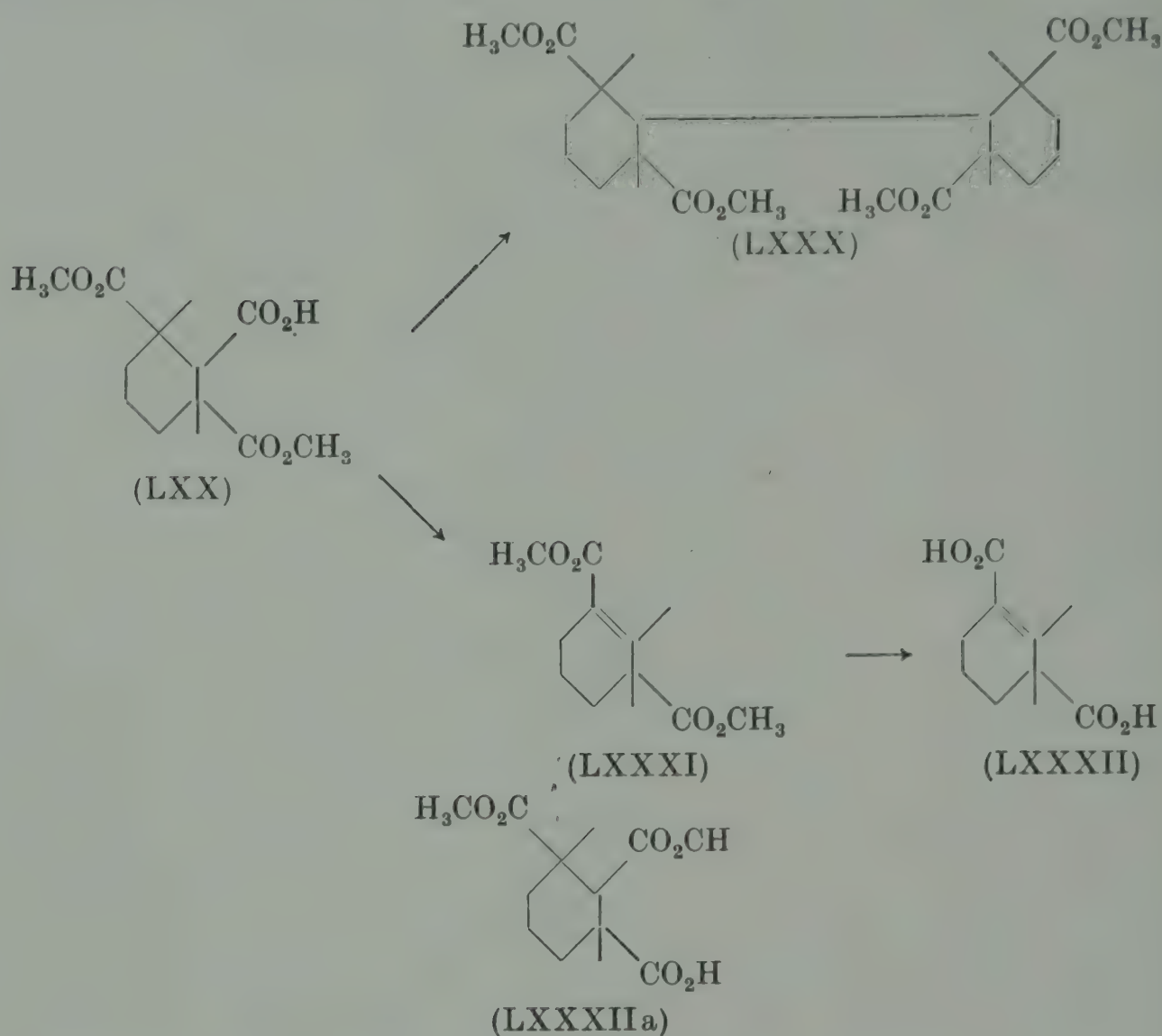
The second asymmetric *dimethyl ester* (LXXXIIa), $C_{13}H_{20}O_6$, m.p. 119–121°, of the tricarboxylic acid (XVI) has recently been prepared by Barton and Schmeidler* by partial alkaline hydrolysis of the corresponding trimethyl ester (XVIa) (see p. 401).



Since both the acids $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_8$ were devoid of optical activity they must be internally compensated and therefore the two carboxyls in the 1:3 position must be in the *cis* relationship to each other. This is confirmed by the facile formation of the 1:3 anhydrides (LXXV), (LXXVI), (LXXVII) and especially (LXXIX), as 1:3 dicarboxylic acids of the *trans* type do not form anhydrides readily and, if formed, they are derived from a *cis* form of the dicarboxylic acid by rearrangement. That a rearrangement had not occurred was shown by the reformation

* J.C.S. 1948, p. 1197.

of the parent acids on hydration. It is not possible to conclude from these experiments whether rings A and C of abietic acid are fused in the *cis* or the *trans* relationship.*



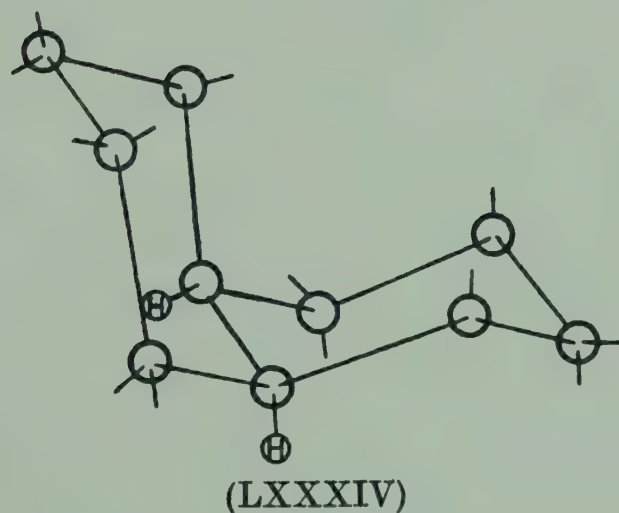
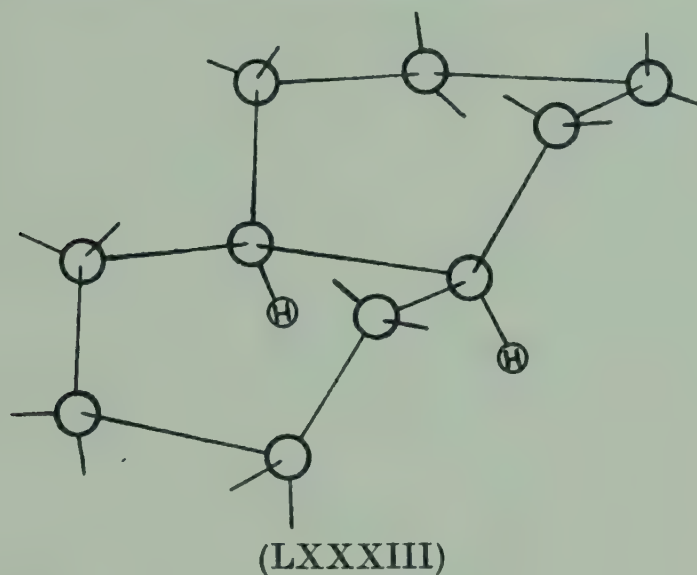
Campbell and Todd,[†] from a study of the properties of podocarpic acid and of dehydroabietic acid (see p. 413), have reached the conclusion that rings A and C in the resin acid series are fused in the *trans* configuration. This, they conclude, provides the only explanation for the relative degree of steric hindrance in podocarpic and dehydroabietic acids and probably also in agathenedicarboxylic acid (see p. 469).

This argument is, however, only valid if the conventional Sachse-Mohr formulation (LXXXIII) for *cis*-decalin be adopted,

* Lombard (*Bull. Soc. Chim.* 1946 [v], 13, 428; *Produits Résineux*, Chapter VI) asserts that the formation of an anhydride m.p. 175° by the action of heat (Lombard, *Thèse de doctorat*, Paris, 1943, p. 43) on the $\text{C}_{11}\text{H}_{16}\text{O}_6$ tricarboxylic acid is a proof that rings A and C of abietic acid are fused in the *cis* position. This is, however, not the case since this anhydride probably has the structure (LXXV) (see p. 403) and is derived from the pair of *cis* related 1:3 carboxyls.

[†] *J. Amer. C.S.* 1942, 64, 928.

and a different interpretation is possible if a model based on the energetically more stable *cis*-decalin (LXXXIV) is assumed. Some evidence in support of the existence of this latter has already been advanced.* The evidence adduced by Zeiss[†] in support of the conclusion of Campbell and Todd[‡] as to the stereochemistry of rings A and C of abietic acid is likewise ambiguous, and the nature of Zeiss' compounds has recently been questioned by Brossi, Gutmann and Jeger.§



The problem of the A/C ring fusion in abietic acid has, however, recently been solved by Barton and Schmeidler^{||}. These authors determined the thermodynamic dissociation constants of the tricarboxylic acid, $C_{11}H_{16}O_6$ (XVI) (see p. 389), and of all its mono- and dimethyl-esters. By methods of calculation, for which the original paper should be consulted, it was proved that

* Bastiansen and Hassel, *Nature*, 1946, **157**, 765; Barton, *J.C.S.* 1948, p. 340; Barton and Miller, *J. Amer. C.S.* 1950, **72**, 1066.

[†] *J. Amer. C.S.* 1947, **69**, 302; 1949, **70**, 858.

[‡] *Loc. cit.*

[§] *Helv. Chim. Acta*, 1950, **33**, 1730.

^{||} *J.C.S.* 1948, p. 1197; 1949, p. S. 232.

the centre carboxyl group in this acid is in the *trans* relationship with respect to its neighbours on either side. Rings A and C of abietic acid are, therefore, likewise fused in the *trans* relationship.*

Abietic acid can be characterised by the formation of the crystalline quarter sodium salt previously referred to on p. 382 and especially, by the optical rotatory power of the acid regenerated from this salt. The optical rotatory power of abietic acid in alcohol has been given on p. 383; the following data refer to other solvents: $[\alpha]_D -103.5^\circ$ (in ether), -103° (in dioxan), -81.0° (in acetic acid), and -70° to -79° (in *cyclohexane*).[†] Abietic acid forms well-characterised crystalline salts with amines and a large number of these have been described, for which reference should be made to the original literature.[‡] Although abietic acid is only esterified with difficulty a number of esters have been prepared, amongst the best characterised being: *methyl*, b.p. $168-172^\circ/0.5$ mm., $d_4^{20^\circ} 1.049$, $n_D^{20^\circ} 1.5346$, *dihydrochloride*, m.p. $163-164^\circ$, *dihydrobromide*, m.p. 148° , and *ethyl*, b.p. $204-207^\circ/4$ mm., $d_4^{13^\circ} 1.032$, $n_D 1.5265$, *dihydrochloride*, m.p. $143-145^\circ$, *dihydrobromide*, m.p. $138-140^\circ$.[§] Abietic acid dihydrochloride (see p. 384) on treatment with acetic acid gives a *monohydrochloride*, m.p. 197° , and the corresponding methyl and ethyl esters behave similarly giving *monohydrochlorides*, m.p.s 126° and $82-84^\circ$ respectively.^{||}

A number of colour reactions have been reported for abietic acid, but none of these is particularly specific.[¶]

* Arbusov and Schapschinskaja (*Ber.* 1935, **68**, 437; *Trans. Kirov. Inst. Chem. Tech. Kazan*, 1935, **3**, 19) have attempted the synthesis of the acid $C_{11}H_{18}O_6$ which would enable this stereochemical problem to be solved. They did not, however, obtain a crystalline product, doubtless because of the presence of several stereoisomerides.

† See Sandermann, *Ber.* 1942, **75**, 174.

‡ Palkin and Harris, *J. Amer. C.S.* 1934, **56**, 1935; compare Dupont and Desalbres, *Bull. Soc. chim.* 1926 [iv], **39**, 492; Balas, *Casopis Cesk. Lekarnictva*, 1927, **7**, 320; Bardyshev, *J. Gen. Chem. U.S.S.R.* 1941, **11**, 996; Krestinskii and Bardyshev, *ibid.* 1940, **10**, 1894.

§ Levy, *Zeit. Angew. Chem.* 1905, **18**, 1740; Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 315; Levy, *Ber.* 1931, **64**, 2441; compare Grün and Winkler, *Chem. Umshau*, 1910, **26**, 77; Virtanen, *Annalen*, 1921, **424**, 189; for other esters of abietic acid see Kesler, Lowy and Faragher (*J. Amer. C.S.* 1927, **49**, 2898; compare Kaufmann and Friedebach, *Ber.* 1922, **55**, 1508).

|| Rau and Simonsen, *Ind. For. Rec.* 1925, **11**, 207; Levy, *Ber.* 1931, **64**, 2441.

¶ Liebermann, *Ber.* 1884, **17**, 1884; Hicks, *Ind. Eng. Chem.* 1911, **3**, 86; Steinle and Kahlenberg, *J. Biol. Chem.* 1926, **67**, 425; Lalande, *J. Amer. C.S.* 1933, **55**, 1536; compare Sans, *Ann. Chim. Anal. Appl.* 1909, **14**, 140.

Mention has already been made of the difference in chemical reactivity shown by the two ethylenic linkages present in abietic acid, and this difference is specially marked in the behaviour of the acid on catalytic hydrogenation, reduction to the saturated acid, tetrahydroabietic acid (see p. 384) requiring somewhat drastic conditions.*

In continuation of earlier experiments by Ruzicka and Meyer,[†] who by the hydrogenation of abietic acid in alcoholic solution using a platinum catalyst prepared a *dihydroabietic acid*, $C_{20}H_{32}O_2$, m.p. 157–159°, $[\alpha]_D + 8^\circ$ (in alcohol), Ruzicka and Kaufmann,[‡] using a palladised calcium carbonate catalyst in methanolic solution, obtained a complex mixture of acids. From this mixture they isolated tetrahydroabietic acid and on subjecting a further fraction, m.p. 120–125°, to oxidation with potassium permanganate they obtained a *dihydroxydihydroabietic acid*, $C_{20}H_{34}O_4$, m.p. 226–227°, $[\alpha]_D - 14^\circ$ (in alcohol), *acetyl* derivative, m.p. 200–201°, *methyl ester*, m.p. 162–163°, $[\alpha]_D - 18^\circ$ (in alcohol). An isomeric *dihydroxydihydroabietic acid*, $C_{20}H_{34}O_4$ (LXXXV), m.p. 225–226°, $[\alpha]_D - 21.5^\circ$ (in alcohol), *acetyl* derivative, m.p. 124–126°, *methyl ester*, m.p. 103–104°, *acetyl* derivative, m.p. 168.5–169.5°, was prepared by the catalytic hydrogenation of dihydroxyabietic acid (XXIX) (p. 391). Neither of these acids lactonised on boiling in toluene solution and it has been suggested that they cannot therefore contain a secondary hydroxyl group at position 9 (compare (XLII), p. 395). It is probable that these dihydroxydihydroabietic acids are not stereoisomers but structural isomers and that the acid, m.p. 226–227°, is to be represented as (LXXXVI).[§] Proof of this structure must await further experiment.

Ruzicka and Kaufmann isolated as a by-product from the potassium permanganate oxidation a *dihydroabietic acid*, m.p. 166–168°, $[\alpha]_D + 10.3^\circ$ (in alcohol), the structure of which is unknown.

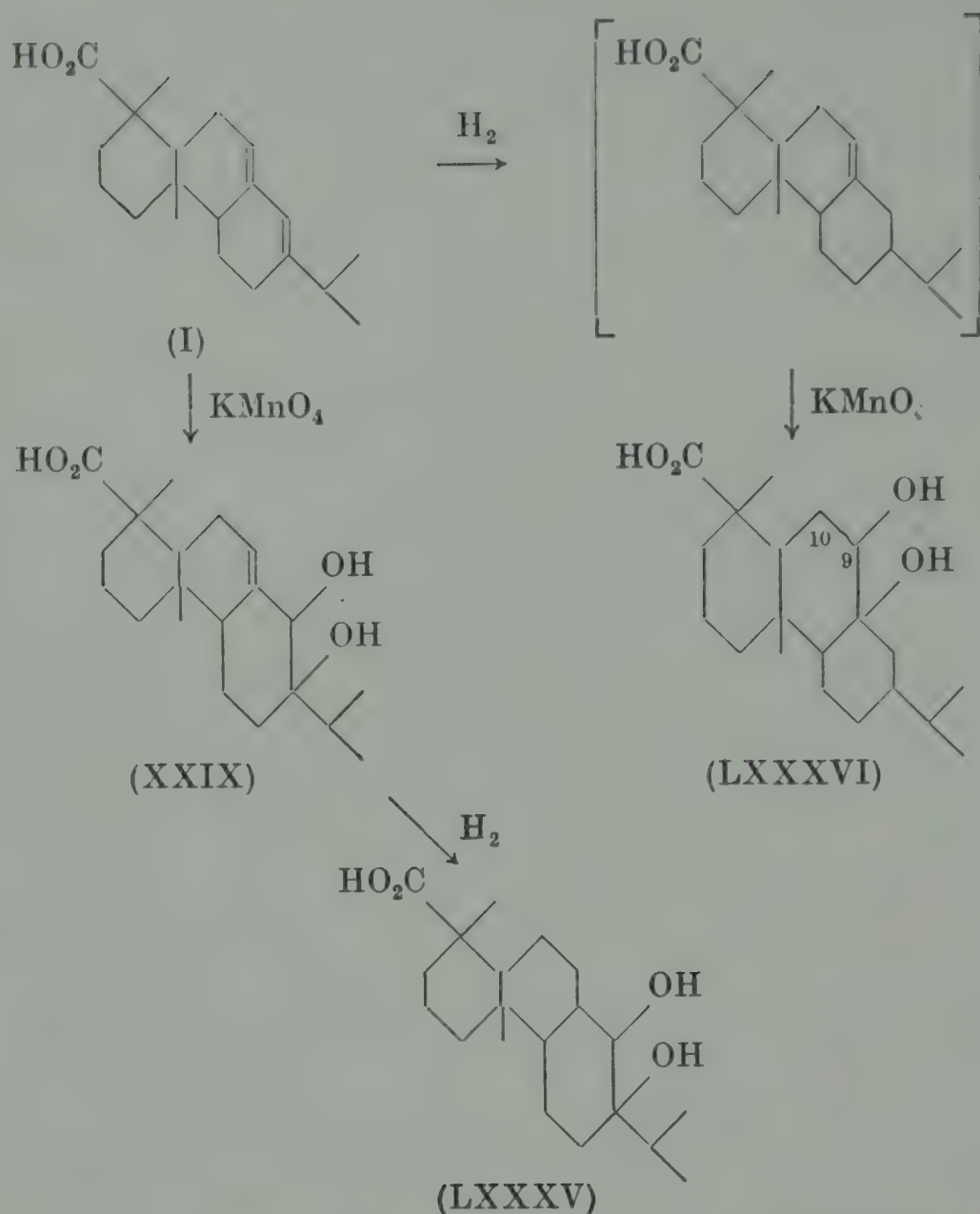
Two further dihydroabietic acids have been obtained from

* Compare Shaefer, *Ind. Eng. Chem., Anal. Ed.*, 1930, **2**, 115.

[†] *Helv. Chim. Acta*, 1922, **5**, 315; compare Johansson, *Arkiv. Kemi Min. Geol.* 1917, **6**, No. 19; Wienhaus, *Zeit. Angew. Chem.* 1921, **34**, 256.

[‡] *Helv. Chim. Acta*, 1941, **24**, 1389.

[§] See, however, Ruzicka and Kaufmann *loc. cit.*



abietic acid. Lombard,* by high-pressure hydrogenation using a palladised charcoal catalyst, prepared a *dihydroabietic acid*, $\text{C}_{20}\text{H}_{32}\text{O}_2$, m.p. 176° , $[\alpha]_D^{20} + 107^\circ$ (in alcohol), which was identical with a dihydroabietic acid isolated earlier by Fleck and Palkin† from pyroabietic acid (see p. 417). The second *dihydroabietic acid*, m.p. $217.5\text{--}218.5^\circ$, $[\alpha]_D - 23^\circ$ (in ether), *diamylamine salt*, m.p. $121.5\text{--}122^\circ$, $[\alpha]_D - 24^\circ$ (in ether), was obtained by Hasselström and McPherson‡ by the action of sodium on abietic acid dihydrobromide.

Lombard§ has recently made a careful study of the products of the partial hydrogenation of abietic acid. Using a platinum catalyst in alcoholic solution α -*dihydroabietic acid*, m.p. 166° , $[\alpha]_D - 26^\circ$ (in alcohol) (possibly LXXXVIa), was obtained. This

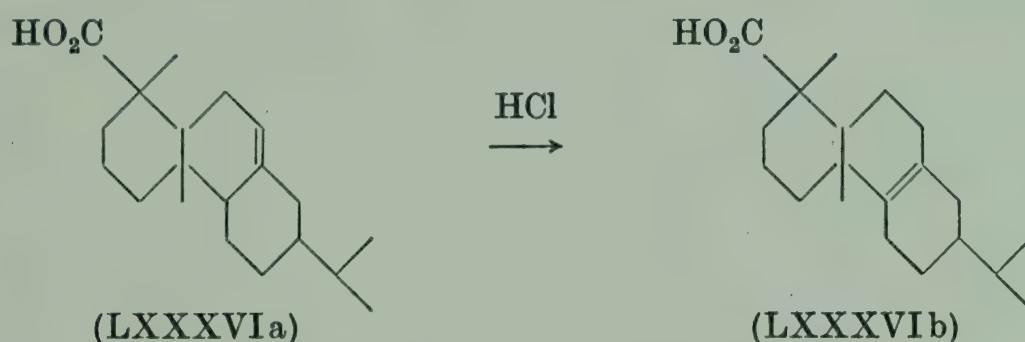
* *Compt. rend.* 1939, **208**, 1321.

† *J. Amer. C.S.* 1938, **60**, 2621.

‡ *Ibid.* 1939, **61**, 1228.

§ *Bull. Soc. Chim.* 1942 [v], **9**, 833; 1944 [v], **11**, 526.

acid could also be prepared by hydrogenation in alcoholic solution using a Raney nickel catalyst at about 130° under pressure. A repetition of the experiment mentioned above on the hydrogenation of abietic acid at high pressure using a palladised charcoal catalyst gave β -dihydroabietic acid, m.p. 175° , $[\alpha]_D + 123^{\circ}$ (in alcohol) (possibly LXXXVIb), in a purer state, as judged by the optical rotatory power, than that obtained previously. By the action of alcoholic hydrochloric acid α -dihydroabietic acid was isomerised to the β -acid.



When the crude mixture of dihydroabietic acids obtained by Ruzicka and Meyer* in their hydrogenation experiments was treated with hydrobromic acid in acetic acid solution a *substance*, $\text{C}_{20}\text{H}_{32}\text{O}_2$, m.p. $130\text{--}131^{\circ}$, $[\alpha]_D$ ca. -2° (in alcohol) resulted. This compound was at first regarded as a dihydroabietic acid, but later investigations† showed that it was a saturated *lactone*, for by vigorous alkaline hydrolysis it afforded a *hydroxytetrahydroabietic acid*,‡ $\text{C}_{20}\text{H}_{34}\text{O}_3$, m.p. $164\text{--}165^{\circ}$, *methyl ester*, m.p. $50\text{--}51^{\circ}$, b.p. $175\text{--}180^{\circ}/2\text{ mm.}$, $[\alpha]_D^{20} + 21^{\circ}$ (in alcohol), from which it was readily regenerated. This lactone has been obtained also§ by the action of cold concentrated sulphuric acid on heat-treated rosin, pyroabietic acid, or any of the dihydroabietic acids or dihydrolevopimaric acids (see p. 438).

It was originally suggested that this lactone was formed from a 10-hydroxytetrahydroabietic acid (LXXXVII) when its structure would be represented by (LXXXVIII).|| This formula is,

* *Helv. Chim. Acta*, 1922, 5, 315.

† Ruzicka, Waldmann, Meier and Hösli, *Helv. Chim. Acta*, 1933, 16, 178; Hasselström and McPherson, *J. Amer. C.S.* 1938, 60, 2340; Hasselström, Brennan and McPherson, *ibid.* 1938, 60, 1267; Fleck and Palkin, *ibid.* 1938, 60, 921, 2621; 1939, 61, 247, 1230, 3197.

‡ See note on nomenclature, p. 391 (footnote).

§ Hasselström, Brennan and McPherson, *loc. cit.*; Fleck and Palkin, *J. Amer. C.S.* 1938, 60, 921; 1939, 61, 3197.

|| Hasselström and McPherson, *J. Amer. C.S.* 1938, 60, 2340.

however, difficult to reconcile with that of abietic acid itself and Fleck and Palkin* have definitely disproved it by the observation that the derived hydroxytetrahydroabietic acid must contain a tertiary alcoholic grouping as shown by its inertness towards acylating and oxidising agents. The most probable formula for the lactone was then considered to be (LXXXIX) but, as Campbell and Todd† have pointed out, such a formulation is only possible if rings A/C are fused in the *cis* relationship. Since it has recently been shown (see p. 405) that this ring fusion is actually *trans*, Barton‡ has suggested that the genesis of the lactone, now formulated as (XC), must involve the migration of the angular methyl group.§

When the lactone was reacted with methyl magnesium iodide it afforded a mixture of two unsaturated acids, $C_{20}H_{32}O_2$ (XCI), m.p. 185–186°, $[\alpha]_D - 36^\circ$ (in alcohol) and (XCII), m.p. 147–148°, $[\alpha]_D + 68^\circ$ (in alcohol). Both these unsaturated acids were stable in boiling acetic acid, but regenerated the lactone on treatment with alcoholic hydrochloric acid. With nitrosyl chloride in acetic acid or with butyl nitrite (XCI) gave, as would be expected, a blue *nitrosolactone* (XCIII), m.p. 91.5–92°, $[\alpha]_D - 925^\circ$ (in alcohol), reduced by sodium sulphide in aqueous alcoholic solution to the corresponding *aminolactone* (XCIV), m.p. 144–145°, $[\alpha]_D + 1^\circ$ (in alcohol). With hot hydrochloric acid in acetic acid solution the lactone (XC) was reformed. The isomeric acid (XCII), in agreement with its assigned formula, afforded the *oximinolactone* (XCV), m.p. 184–185°, $[\alpha]_D - 30^\circ$ (in chloroform) under the same conditions. With mineral acid this oximinolactone (XCV) underwent the Beckmann change, but the products have not been identified. It will be noted that neither of these acids is identical with any of the dihydroabietic acids previously discussed (see above and compare p. 437), which non-identity may be taken to support their present formulation.

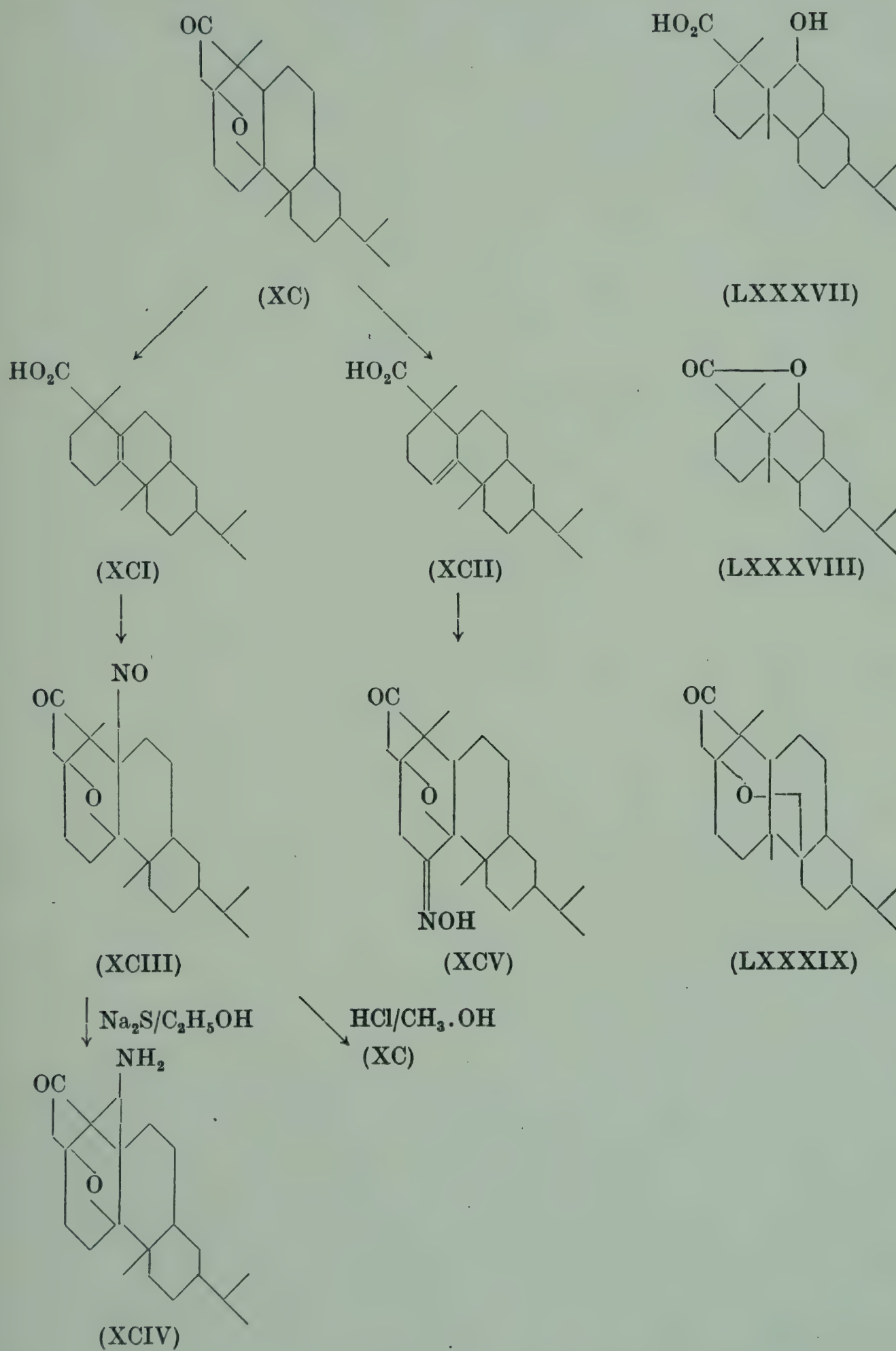
Although much attention has been devoted to the autoxidation of abietic acid, its salts and its esters, no homogeneous products

* *J. Amer. C.S.* 1939, **61**, 3197.

† *Ibid.* 1942, **64**, 928.

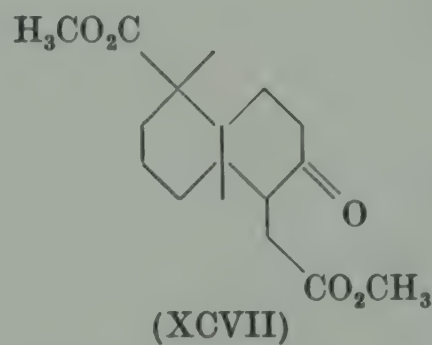
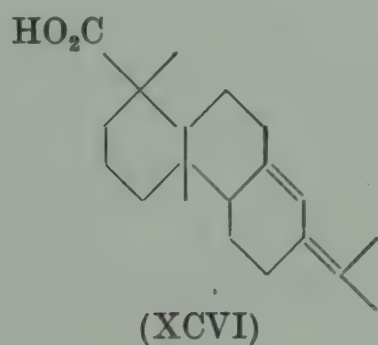
‡ *Chem. and Ind.* 1948, p. 638.

§ Such migrations are well known in the steroid field, e.g. the formulation of Westphalen's diol (Westphalen, *Ber.* 1915, **48**, 1064; Petrow, *J.C.S.* 1937, p. 1077; Petrow, Rosenheim and Starling, *ibid.* 1938, p. 677; Petrow, *ibid.* 1939, p. 998). This formula also explains without difficulty the experimental results of Cox (*J. Amer. C.S.* 1944, **66**, 865) described below.



would appear to have been isolated.* Reference has already been made (p. 387) to some of the more important products resulting from the ozonolysis of abietic acid. Under less vigorous reaction conditions Ruzicka and Meyer[†] obtained by the action of ozone on abietic acid a *triozonide*, m.p. 91–93° decomp., on dihydroabietic acid a *diozonide*, m.p. 97–102° decomp., and on tetrahydroabietic acid a *monozonide*, m.p. ca. 97–99°. Under somewhat more vigorous conditions Raudnitz, Lederer and Kahn,[‡] by ozonolysis of abietic acid, reported the formation of about 3 per cent. of acetone, which they suggested was derived from a small proportion of the double bond isomer of abietic acid (XCVI) present in the sample they used.

By prolonged ozonolysis methyl abietate afforded, after suitable esterification of the mixed reaction products, one fraction containing a probably inhomogeneous *dimethyl ester*, $C_{17}H_{26}O_5$, b.p. 180°/0.2 mm., giving the reactions of a ketone and thought to be represented by (XCVII).[§] The same substance was also obtained by Kraft^{||} by ozonolysis of a sapinic acid from the oleoresin of *Pinus palustris*.



By oxidation of abietic acid with selenium dioxide Fieser and Campbell[¶] prepared 6-hydroxyabietic acid, $C_{20}H_{30}O_3$ (XCVIII),

* *Inter al.* Dupont and Dubourg, *Bull. Inst. Pin*, 1928, **52**, 205; Dupont and Levy, *Compt. rend.* 1929, **189**, 763, 920; Dupont and Levy, *Bull. Soc. chim.* 1930 [iv], **47**, 60; Dupont and Allard, *Compt. rend.* 1930, **190**, 1419; Dupont and Levy, *Chimie et Industrie*, 1930, Special No., p. 428; Dupont, Levy and Allard, *Compt. rend.* 1930, **190**, 1302; Dupont and Levy, *Bull. Soc. chim.* 1930 [iv], **47**, 147; *Bull. Inst. Pin*, 1930, p. 248; Dupont, Levy and Allard, *Bull. Soc. chim.* 1930 [iv], **47**, 942; Dupont and Allard, *ibid.* 1930 [iv], **47**, 1216; Lalande, *J. Amer. C.S.* 1931, **53**, 1858; Dupont and Allard, *Chimie et Industrie*, 1932, **27**, 661; Malevskaya and Kazeeva, *Zhur Priklad. Khim.* 1948, **21**, 854; *Chem. Abs.* 1949, **43**, 6185.

[†] *Helv. Chim. Acta*, 1922, **5**, 315; compare Harries, *Zeit. Angew. Chem.* 1922, **33**, 322; Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 637.

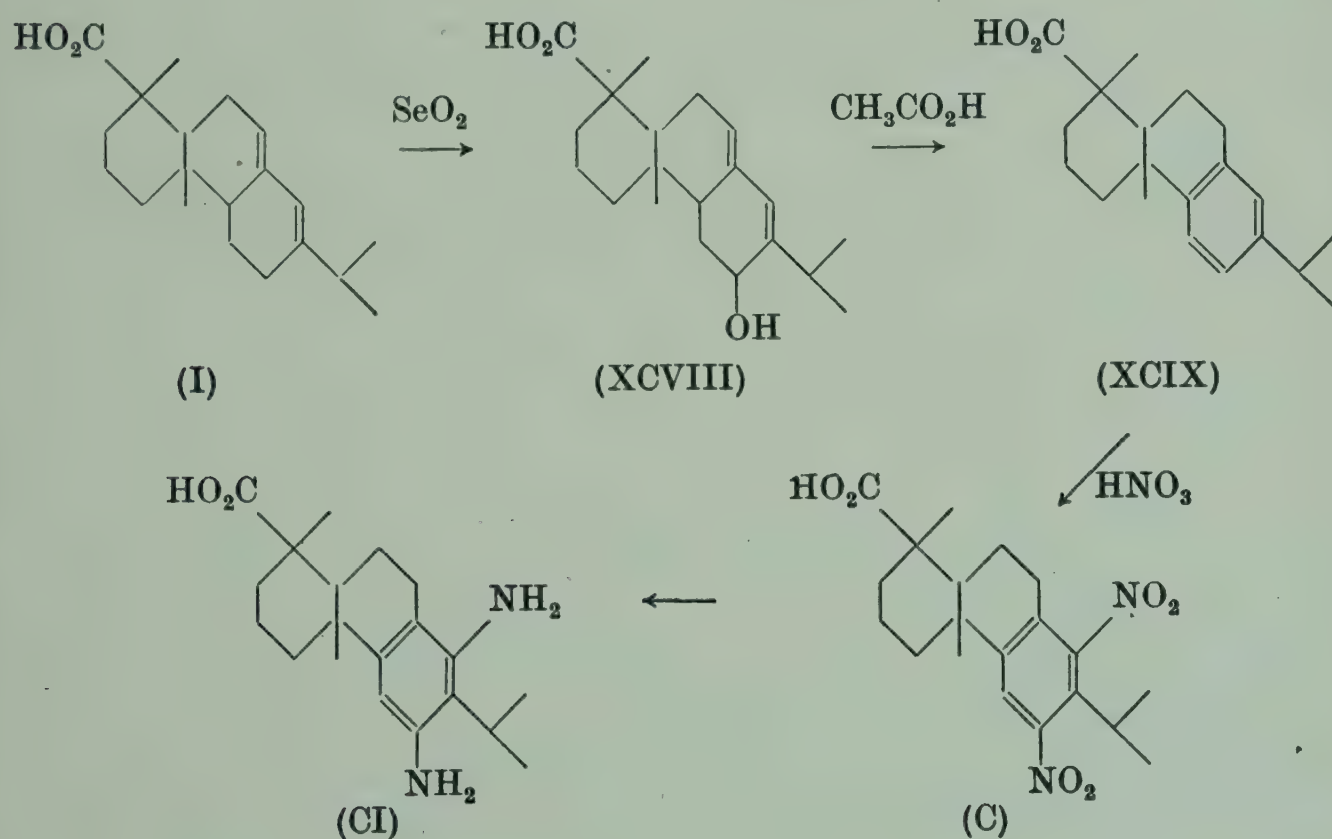
[‡] *Ber.* 1938, **71**, 1273.

[§] Ruzicka, Meyer and Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 637; Ruzicka, Waldmann, Meier and Hösli, *ibid.* 1933, **16**, 169.

^{||} *Annalen*, 1935, **520**, 133.

[¶] *J. Amer. C.S.* 1938, **60**, 159.

m.p. 153–155°, $[\alpha]_D -125^\circ$ (in alcohol), *hemihydrate*, m.p. 120–130° decomp., *sodium salt*, $(C_{20}H_{30}O_3)_3 \cdot C_{20}H_{29}O_3Na \cdot 2H_2O$, m.p. 167–170° decomp., $[\alpha]_D^{25^\circ} -144^\circ$ (in alcohol), *methyl ester*, m.p. 75–77.5°, $[\alpha]_D -96^\circ$ (in alcohol). The structure of this acid was established by its oxidation with potassium permanganate to *isobutyric acid* and by its failure to yield a lactone. On catalytic hydrogenation it gave a mixture of dihydro-acids, m.p. 157°, whilst by boiling with acetic acid *dehydroabietic acid*, $C_{20}H_{28}O_2$ (XCIX), m.p. 171–172°, $[\alpha]_D^{25^\circ} +64^\circ$ (in alcohol), $+76^\circ$ (in benzene), *methyl ester* (XCIXa), m.p. 62–62.5°, $d_4^{99^\circ} 1.0013$, $n_D^{99^\circ} 1.5081$, $[\alpha]_D +67.5^\circ$ (in benzene), λ_{\max} 269 and 275 $m\mu$ with $\log \epsilon = 2.9^*$ was obtained. This acid is more



conveniently prepared using N-bromsuccinimide.[†] Nitration afforded 6:8-dinitrodehydroabietic acid, $C_{20}H_{26}O_6N_2$ (C), m.p. 178–185° decomp., $[\alpha]_D^{25^\circ} +49^\circ$ (in acetone), *methyl ester*, m.p. 189–189.5°, $[\alpha]_D^{25^\circ} +53^\circ$ (in acetone). This dinitro-acid was identical with an acid prepared previously by Johansson[‡] and by Virtanen[§] by nitration of specimens of so-called abietic acid

* Compare Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, 1938, 21, 591.

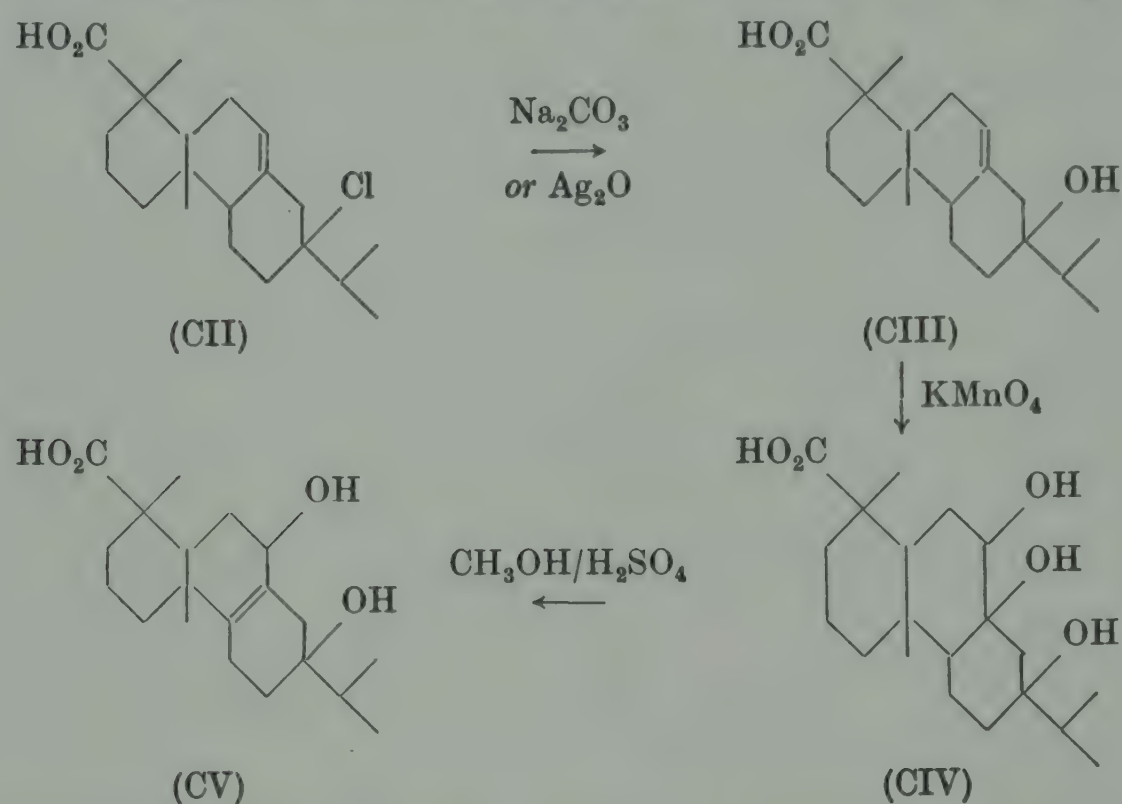
† Jeger, Dürst and Büchi, *Helv. Chim. Acta*, 1947, 30, 1853.

‡ *Arkiv. Kemi Min. Geol.* 1917, 6, No. 19.

§ *Annalen*, 1921, 424, 150.

possessing low laevorotation (see pp. 381–3).* On high-pressure hydrogenation using a copper chromite catalyst 6:8-*diamino-dehydroabietic acid*, $C_{20}H_{30}O_2N$ (CI), *methyl ester*, m.p. 133–134°, was obtained.†

By digesting abietic acid monohydrochloride, probably (CII) (see p. 406), with sodium carbonate Rau and Simonsen‡ prepared a *monohydroxyabietic acid*, $C_{20}H_{32}O_3$ (probably (CIII)), m.p. 230°,



methyl ester, m.p. 110°. Levy§ obtained by the use of silver oxide the same hydroxy acid, whilst by the action of alcoholic potassium hydroxide on abietic acid dihydrobromide he prepared an isomeric *monohydroxyabietic acid*, $C_{20}H_{32}O_3$, m.p. ca. 154°.|| When the monohydroxyabietic acid (CIII) was oxidised with potassium permanganate it afforded a *trihydroxyabietic acid*, $C_{20}H_{34}O_5$ (CIV), m.p. 210–212°, *methyl ester*, m.p. 172°, which was dehydrated by methyl alcoholic sulphuric acid with production of a *dihydroxyabietic acid*, $C_{20}H_{32}O_4$, m.p. 278°, *methyl ester*, m.p. 144°, *acetate*, m.p. 186°, which may possibly be represented by (CV).

The formation of trimellitic acid and of the tricarboxylic acids $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_6$, by the oxidation of abietic acid with

* 6:8-Dinitrodehydroabietic acid can also be prepared by nitration of pyroabietic acid; compare p. 417.

† Littmann, *J. Amer. C.S.* 1938, **60**, 1419.

‡ *Ind. For. Rec.* 1925, **11**, 207.

§ *Ber.* 1931, **64**, 2441.

|| However, compare the preparation of *isoabietic acid*, p. 426.

nitric acid, has already been referred to on p. 387. According to Levy* abietic acid and its derivatives yield also $\beta:\beta$ -dinitropropane on oxidation with nitric acid. Goldblatt† found that treatment of abietic acid with nitric acid in alcoholic solution afforded a dinitro-acid, m.p. 171° , $[\alpha]_D^{20} -118^\circ$ (in alcohol), ethyl ester, m.p. 157.5 – 157.8° , to which he gave the formula $C_{19}H_{26}O_6N_2$. It would appear doubtful if this can be correct. This acid had been prepared previously in a somewhat less pure state by Dubourg,‡ who claimed that on further nitration with fuming nitric acid it gave a trinitro-acid, m.p. 156 – 158° , $[\alpha]_D -136.4^\circ$, to which he gave the improbable formula, $C_{17}H_{17}O_8N_3$. It has also been claimed by Dubourg that a trinitro-acid, $C_{20}H_{27}O_8N_3$, m.p. 177 – 178° , $[\alpha]_D -95^\circ$ is formed by the action of nitric acid on abietic acid in carbon tetrachloride solution.

The oxidation of abietic acid by mercuric acetate was examined by Rouin,§ who found that a monocarboxylic acid, $C_{20}H_{28}O_4$, m.p. 198 – 200° , $[\alpha]_D +29.8^\circ$ (in alcohol) was formed. The constitution of this acid is unknown, although Rouin suggested that it was either a diketone or a ketonic oxide.

The action of heat on colophony and on abietic acid has been frequently studied. In recent years the nature of the products thus formed has been considerably clarified. The isomerisation of the primary resin acids of colophony by distillation has been already mentioned on p. 381, and the effect of more drastic heat treatment is discussed below. According to Dupont, Rouin and Dubourg|| pure abietic acid as usually described is a hydrate $4C_{20}H_{30}O_2 \cdot H_2O$, and the anhydrous acid prepared therefore by heating *in vacuo* has the lower melting-point of 151 – 153° . This view does not seem, however, to be generally accepted and, for example, Fonrobert¶ held that this acid was simply impure abietic acid formed by slight autoxidation under the drying conditions used by the French authors. Moreover, Schwalbe** has asserted that abietic acid begins to lose carbon dioxide even at 120° .

* Ber. 1929, 62, 2497.

† J. Amer. C.S. 1930, 52, 2132.

‡ Bull. Inst. Pin, 1927, 41, 241; 1929, 59, 138; compare Easterfield and Bagley, J.C.S. 1904, 85, 1238.

§ Bull. Inst. Pin, 1930, p. 155; compare Powell, Paint, Oil Chem. Rev. 1929, 7, 12.

|| Bull. Inst. Pin, 1927, 38, 157; 1927, 35, 97.

¶ Chem. Umschau, 1929, 36, 373.

** Zeit. Angew. Chem. 1905, 18, 1852.

In the production of colophony (see p. 375) a final temperature of about 160° is used, and at one time it was a matter of acute controversy as to whether at this temperature anhydrides of the resin acids were not formed. Maly* was the first to suggest that colophony was a mixture of anhydrides and this view was supported by Flückiger,[†] Bischoff and Nastvogel,[‡] Fahrion[§] and more especially by Knecht.^{||} However, the careful experiments of Ruzicka and Schinz[¶] and of Ruzicka and Pfeiffer** have definitely disproved this and the properties of *abietic anhydride*, $C_{40}H_{58}O_3$, m.p. 149° , $[\alpha]_D -18^{\circ}$ (in benzene), prepared by Fonrobert and Pallauf,^{††} are quite different from those of colophony. The investigations of Lalande^{‡‡} would seem to prove that no anhydride formation from abietic acid can occur at about 160° and that water is only slowly lost at 230° with formation of the anhydride.^{§§}

It has been claimed^{|||} that on sublimation abietic acid is converted into an isomeric acid, m.p. 150° , $[\alpha]_D^{25^{\circ}} -35.1^{\circ}$ (in alcohol), which is very much more stable than abietic acid itself. There is no indication as to the structure of this alleged isomer, but it is conceivably a mixture of abietic acid and neoabietic acid (see p. 445).

There is frequent reference in the literature to a *pyroabietic acid* considered to be an isomer of abietic acid and said to be formed by heating levopimaric acid, abietic acid or colophony

* *Annalen*, 1868, **149**, 244.

† *J. pr. Chem.* 1867, **101**, 235.

‡ *Ber.* 1890, **23**, 1919.

§ *Zeit. Angew. Chem.* 1902, **15**, 83.

|| Knecht and Hibbert, *J. Soc. Dyers and Colourists*, 1919, **35**, 148; Knecht, *ibid.* 1925, **41**, 329.

¶ *Helv. Chim. Acta*, 1923, **6**, 833.

** *Ibid.* 1925, **8**, 632; compare Labatut, *Soc. de Sci. de Bordeaux*, 20th March 1920; Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 329; Schorger, *J. Amer. C.S.* 1923, **45**, 1339; Shaw and Sebrell, *Ind. Eng. Chem.* 1926, **19**, 612; Rouin, *Bull. Inst. Pin*, 1929, **59**, 124.

†† *Farben Ztg.* 1926, **31**, 1848; Fonrobert, *Chem. Umschau*, 1929, **36**, 93, 373; Nagel, *ibid.* 1929, **36**, 33; compare, however, Dupont, Dubourg and Rouin, *Bull. Inst. Pin*, 1927, **35**, 97; *Chimie et Industrie*, 1927, p. 1691; Dupont, Dubourg and Rouris, *Monit Produits Chim.* 1936, **18**, No. 211, p. 8.

‡‡ *Ind. Eng. Chem.* 1934, **26**, 678.

§§ Compare, however, Rouin, *Bull. Inst. Pin*, 1928, **53**, 221.

||| Lalande, *Ind. Eng. Chem.* 1934, **26**, 678; Lipkin and Lalande, *J. Amer. C.S.* 1936, **58**, 1310; compare Labatut and Duffour, *Soc. de Sc. de Bordeaux*, 1919, p. 31; Dupont, *Bull. Soc. chim.* 1924 [iv], **35**, 1209; Shaw and Sebrell, *Ind. Eng. Chem.* 1926, **18**, 612.

at 250–300° for long periods of time.* Various melting-points ranging from *ca.* 157° to *ca.* 170°, $[\alpha]_D$ *ca.* +40° to *ca.* +60° (in alcohol) were recorded, whilst Fanica[†] suggested that there were two, α - and β -pyroabietic acids, respectively dextrorotatory and laevorotatory. It was, however, shown that the so-called β -pyroabietic acid was a mixture of abietic acid and the dextrorotatory α -acid.‡ Improved methods for the preparation of pyroabietic acid involving the use of catalysts such as palladised charcoal[§] or iodine^{||} have been introduced, whilst partial dehydrogenation of abietic acid with sulphur is also said to be effective.[¶]

It was first suggested by Fieser and Campbell^{**} that pyroabietic acid was not homogeneous but a disproportionation mixture of dehydroabietic acid (XCIX) (see p. 413), dihydroabietic acids and tetrahydroabietic acid (III) (see p. 384). This suggestion was subsequently fully confirmed. By fractional crystallisation of pyroabietic acid Ruzicka, Bacon, Sternbach and Waldmann^{††} separated a *dihydroabietic acid*, C₂₀H₃₂O₂, m.p. 193–194°, $[\alpha]_D$ +9.0° (in alcohol), +13.5° (in chloroform), which could be reduced by catalytic hydrogenation to tetrahydroabietic acid.^{‡‡} A different *dihydroabietic acid*, m.p. 174–176°, $[\alpha]_D^{20}$ +108° (in alcohol) was obtained by Fleck and Palkin,^{§§} and this is doubtless identical with a dihydroabietic acid prepared later by the direct hydrogenation of abietic acid (see p. 408). These authors^{|||} also

* *Inter al.* Bischoff and Nastvogel, *Ber.* 1890, **23**, 1919; Schulz, *Chem. Ztg.* 1917, **41**, 666; Ruzicka and Meyer, *Helv. Chim. Acta*, 1922, **5**, 338; Dupont and Dubourg, *Bull. Inst. Pin*, 1926, **27**, 479; 1928, **51**, 181; Rouin, *ibid.* 1928, **51**, 221; Fonrobert and Greth, *Chem. Umschau*, 1929, **36**, 93; Lalande, *Ind. Eng. Chem.* 1934, **26**, 679; Dupont and Dubourg, *Monit. Produits Chim.* 1936, **18**, No. 211, p. 11; Ruzicka, Bacon, Sternbach and Waldmann, *Helv. Chim. Acta*, 1938, **21**, 591; Garkuska, *J. Gen. Chem. U.S.S.R.* 1938, **8**, 1042; Lombard, *Bull. Soc. chim.* 1942 [v], **9**, 833.

† *Bull. Inst. Pin*, 1933, **44**, 151; 1933, **44**, 151; 1933, **45**, 181; compare Klason and Kohler, *J. pr. Chem.* 1906 [ii], **73**, 337; Greth, *Chem. Umschau*, 1929, **36**, 36; Fonrobert and Greth, *ibid.* 1929, **36**, 93.

‡ Greth, *Zeit. Angew. Chem.* 1934, **47**, 827; Lombard, *Bull. Soc. chim.* 1942 [v], **9**, 833.

§ Fleck and Palkin, *Science*, 1937, **85**, 126; *J. Amer. C.S.* 1937, **59**, 1593; compare Littman, *ibid.* 1938, **60**, 1419; Lombard, *Compt. rend.* 1939, **208**, 1321; Eukvist, *Finska Kemists. Medd.* 1942, **51**, 40.

|| Hasselström, Brennan and Hopkins, *J. Amer. C.S.* 1941, **63**, 1759.

¶ Lombard, *Compt. rend.* 1941, **213**, 793; *Bull. Soc. chim.* 1942 [v], **9**, 833; Dupont, Dulow and Devillers, *Bull. Soc. chim.* 1949 [v], **16**, 315.

** *J. Amer. C.S.* 1938, **60**, 159.

†† *Helv. Chim. Acta*, 1938, **21**, 591.

‡‡ From the later experiments of Hasselström and McPherson (*J. Amer. C.S.* 1939, **61**, 1228; compare Brennan, Cairncross, Hasselström and Hull, U.S.P. 2, 272, 628) it would appear doubtful if this dihydroabietic acid were homogeneous.

§§ *J. Amer. C.S.* 1937, **59**, 1593.

||| *Ibid.* 1938, **60**, 921.

separated from pyroabietic acid a *tetrahydroabietic acid*, $C_{20}H_{34}O_2$, m.p. 183–184°, $[\alpha]_D^{20} + 6^\circ$ (in alcohol), *methyl ester*, m.p. 44–45°.* Fleck and Palkin† studied the effect of temperature on the palladised charcoal catalysed formation of dehydroabietic acid and found that whilst the reaction at 225° is mainly one of disproportionation, that at higher temperatures proceeds also by a partial dehydrogenation mechanism, gaseous hydrogen being evolved. There seems also to be a difference between the disproportionation products of abietic acid depending upon whether a palladium catalyst is used in the preparation or not. Thus it has only been possible to detect the dihydroabietic acid, m.p. 174–176°, $[\alpha]_D^{20} + 108^\circ$ (in alcohol), in pyroabietic acids prepared in the presence of a catalyst, although dihydroabietic acids are certainly present in pyroabietic acid prepared by simple heat treatment as is shown by reaction with cold concentrated sulphuric acid (see below).‡

By treatment of pyroabietic acid with cold concentrated sulphuric acid it is possible to identify the presence in it of both dihydro- and dehydroabietic acids. The former yields the saturated lactone, the constitution of which is discussed on p. 409,§ whereas the latter is sulphonated giving *dehydroabietic acid 6-sulphonic acid* (CVI), *hemihydrate*, m.p. 247–248° decomp., *trihydrate*, m.p. 223–224° decomp., $[\alpha]_D^{25} + 72.4^\circ$ (in alcohol), *dimethyl ester*, m.p. 175–176°, $[\alpha]_D^{25} + 76.2^\circ$ (in alcohol), *diethyl ester*, m.p. 150.4–151.4°, *diamide*, m.p. 254–255.5°, *p-toluidine salt*, m.p. 271° decomp., $[\alpha]_D^{25} + 57^\circ$ (in alcohol), is easily isolated.|| The position of the sulphonic acid group in this substance has been proved by the experiments of Campbell and Morgana.¶ This sulphonic acid is easily reconverted to dehydroabietic acid by acid hydrolysis, a process which constitutes the best method for the preparation of dehydroabietic acid in a state

* Compare p. 384 and see also Littmann, *J. Amer. C.S.* 1938, **60**, 1419.

† *Ibid.* p. 921.

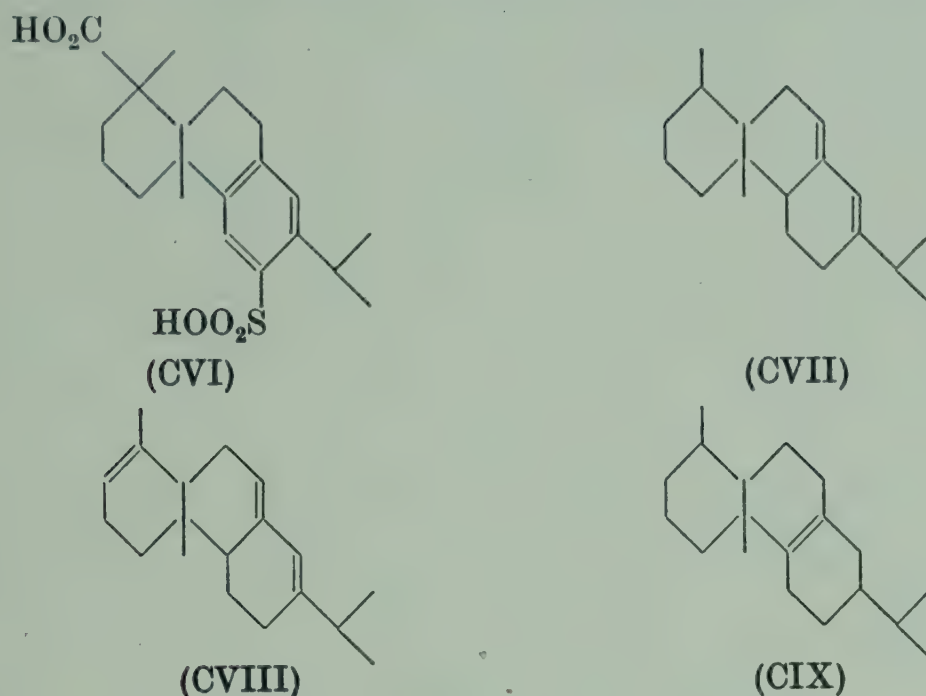
‡ Fleck and Palkin, *ibid.* 1939, **61**, 247.

§ Fleck and Palkin, *ibid.* 1938, **60**, 921, 2621; Hasselström, Brennan and McPherson, *ibid.* 1938, **60**, 1267; Hasselström and McPherson, *ibid.* 1938, **60**, 2340.

|| Hasselström, Brennan and McPherson, *J. Amer. C.S.* 1938, **60**, 1267; Hasselström and McPherson, *ibid.* 1938, **60**, 2340; Fieser and Campbell, *ibid.* 1938, **60**, 2631; compare Fanica, *Bull. Inst. Pin*, 1933, **44**, 151; 1933, **45**, 181; Greth, *Zeit. Angew. Chem.* 1934, **47**, 927.

¶ *J. Amer. C.S.* 1941, **63**, 1838.

of purity.* The synthesis of *dl*-dehydroabietic acid or of a stereoisomeride thereof has been described by Haworth and Barker.†



When abietic acid or colophony is dry distilled or distilled under about 10 to 20 mm. pressure decomposition occurs with loss of the carboxyl group. To a certain extent this reaction also occurs during the preparation of pyroabietic acid, especially in the absence of a catalyst. The nature of the products thus formed has been the subject of considerable study.‡

The product obtained is not simply the hydrocarbon, *abietene*, C₁₉H₃₀, possibly (CVII), formed from abietic acid by decarboxylation, but consists of a hydrocarbon mixture since, in addition to carbon dioxide, the gaseous products contain carbon monoxide and a little hydrogen and methane. One of the hydrocarbons found in the mixture is *abietin*, C₁₉H₂₈, possibly (CVIII). A typical mixture, obtained by heating abietic acid at 300°, had b.p. 143–145°/0.1 mm., d_4^{19} 0.9672, n_D^{19} 1.5318, $[\alpha]_D + 99.4^\circ$, whilst a specimen prepared from American colophony had very similar physical properties, b.p. 142–144°/0.1 mm.,

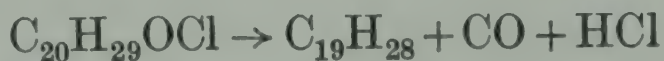
* Fieser and Campbell, *J. Amer. C.S.* 1938, **60**, 2631; 1939, **61**, 2528.

† *J.C.S.* 1939, p. 1299.

‡ *Inter al.* Deville, *Annalen*, 1841, **37**, 193; Renard, *Compt. rend.* 1887, **104**, 665; Kramer and Spilker, *Ber.* 1899, **32**, 2953; Kramer, *Ber.* 1899, **32**, 3614; 1900, **33**, 2267; 1903, **36**, 647; Easterfield and Bagley, *J.C.S.* 1904, **85**, 1246; Levy, *Ber.* 1906, **39**, 3043; Ruzicka and Schinz, *Helv. Chim. Acta*, 1923, **6**, 833; compare Kelbe, *Ber.* 1880, **13**, 888; Bamberger and Strasser, *Ber.* 1889, **22**, 3368; Henry, *J.C.S.* 1901, **79**, 1144; Schwalbe, *Zeit. Angew. Chem.* 1905, **18**, 1852; Tschirch and Wolff, *Arch. Pharm.* 1907, **245**, 1; Levy, *Ber.* 1907, **40**, 3658; Schultze, *Annalen*, 1908, **359**, 129; Henze, *Ber.* 1916, **49**, 1622; Virtanen, *Annalen*, 1921, **424**, 209.

$d_4^{19^\circ}$ 0.9641, $n_D^{19^\circ}$ 1.5326, $[\alpha]_D + 110.3^\circ$.^{*} By catalytic hydrogenation of the mixed hydrocarbons from American colophony *dihydroabietene*, $C_{19}H_{32}$, possibly (CIX), b.p. 145–146°/0.1 mm., $d_4^{16^\circ}$ 0.9470, $n_D^{16^\circ}$ 1.5135, was obtained.[†] This latter hydrocarbon was not identical with a hydrocarbon of the same formula prepared by Easterfield and Bagley[‡] by reduction of abietic acid with red phosphorus and hydrogen iodide.[§] The investigations which have been carried out on these hydrocarbons were all effected prior to the elucidation of the structures of abietic acid and dehydroabietic acid. The conclusions reached probably require, therefore, drastic revision.

When abietic acid chloride, which has not been described in a state of purity, is distilled, decomposition occurs according to the equation



with production of abietin, b.p. 200–202°/17 mm., contaminated apparently with but little abietene.^{||}

Rouin[¶] has studied the action of molten zinc chloride on abietic acid, the product of the reaction being regarded as an *octahydroretene*, $C_{18}H_{26}$, b.p. 202–203°/15 mm., $d_{15}^{15^\circ}$ 0.955, $n_D^{17^\circ}$ 1.5230, $[\alpha]_D \pm 0^\circ$, whose structure is unknown.

The effect of sodium hydroxide on abietic acid at 240–280° has been examined by Berger.^{**} He obtained a mixture of a *hydrocarbon*, $C_{18}H_{22}$, m.p. 104°, $[\alpha]_D^{50^\circ} + 106^\circ$ (in methanol), presumably a tetrahydroretene, and a second hydrocarbon which was probably impure retene. The suggestion of Berger that the $C_{18}H_{22}$ hydrocarbon may be 2:2':3-*trimethyl-4'-isopropyldiphenyl* must be incorrect in view of the high rotatory power.

Fieser and Campbell^{††} observed that methyl dehydroabietate underwent a smooth Friedel-Crafts reaction to furnish a mixture of 6-*acetyldehydroabietic acid methyl ester* (CX), m.p. 133.5–134°,

* The high dextrorotation of these substances together with their method of preparation suggests that they are at least partly aromatic in Ring B, like dehydroabietic acid, see p. 413.

† Ruzicka and Schinz, *Helv. Chim. Acta*, 1923, **6**, 833.

‡ *Loc. cit.*

§ Compare Liebermann and Spiegel, *Ber.* 1889, **22**, 780.

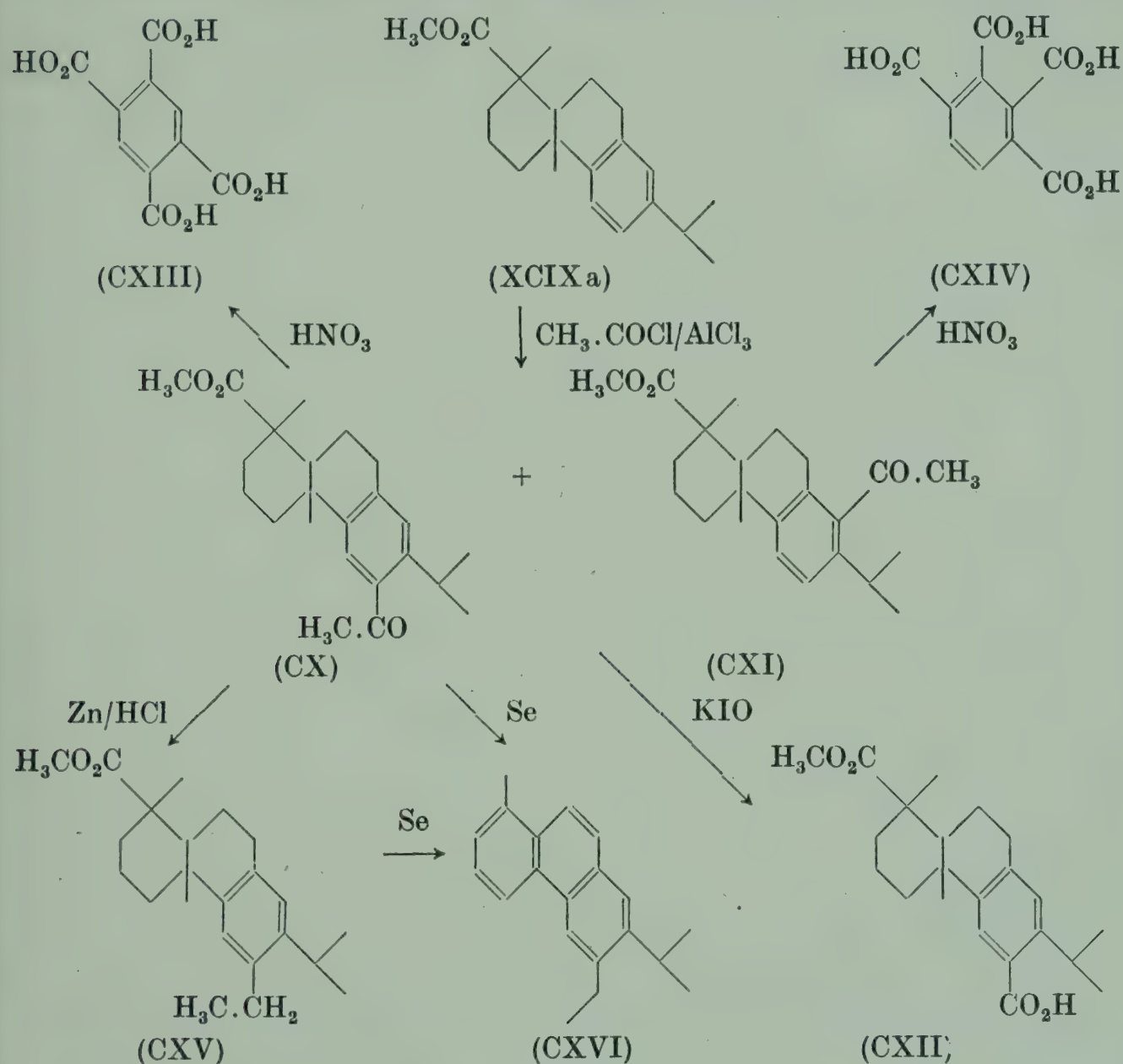
|| Levy, *loc. cit.*; compare Virtanen, *loc. cit.*

¶ *Bull. Inst. Pin.*, 1929, p. 251; compare Emmerling, *Ber.* 1879, **12**, 1444.

** *J. pr. Chem.* 1932 [ii], **133**, 331.

†† *J. Amer. C.S.* 1938, **60**, 2631; 1939, **61**, 2528.

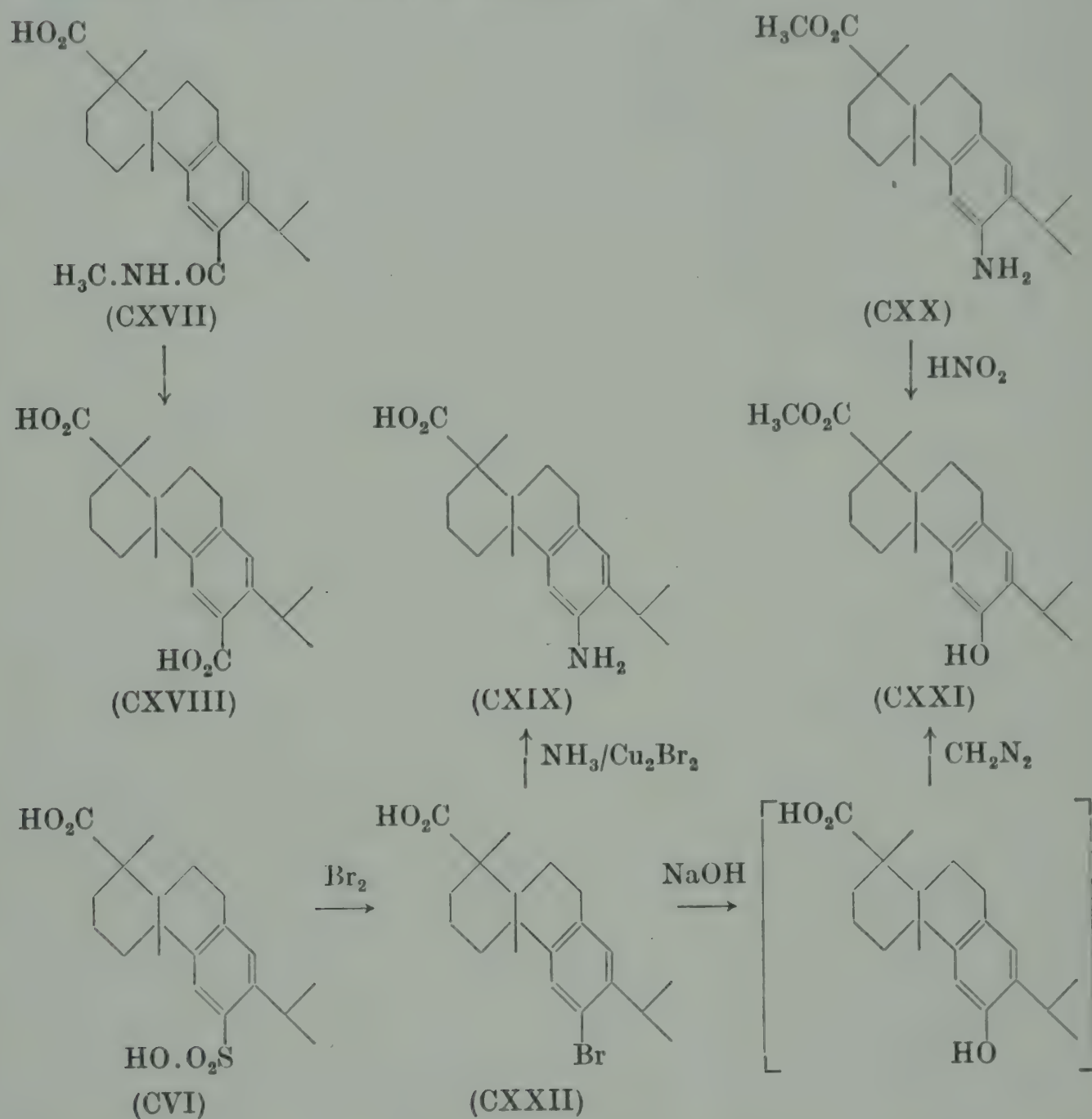
$[\alpha]_D^{25} + 57^\circ$ (in alcohol), *methyl ester oxime*, m.p. $151.5\text{--}152^\circ$, $[\alpha]_D^{25} + 83^\circ$ (in alcohol), and *8-acetyldehydroabietic acid methyl ester* (CXI), m.p.s 137° and $153\text{--}153.5^\circ$ (dimorphic forms), $[\alpha]_D^{25} + 40^\circ$ (in alcohol). On hydrolysis (CX) afforded *6-acetyldehydroabietic acid*, m.p. $174.5\text{--}175^\circ$, $[\alpha]_D^{25} + 74^\circ$ (in alcohol), which on oxidation with potassium hypoiodite was converted into *methyl 6-carboxydehydroabietate* (CXII), m.p. $190\text{--}191.5^\circ$,



$[\alpha]_D^{25} + 74^\circ$ (in alcohol). The positions of the entrant acetyl group were proved by oxidation with nitric acid when (CX) gave *pyromellitic acid* (CXIII), and (CXI) furnished *prehnitic acid* (CXIV). Shortly afterwards Ruzicka and Kaufmann* converted methyl 6-acetyldehydroabietate (CX), by reduction by Clemmensen's method, to *methyl 6-ethyldehydroabietate* (CXV), $\text{C}_{23}\text{H}_{34}\text{O}_2$, m.p. $94.5\text{--}95^\circ$, $[\alpha]_D + 60^\circ$ (in chloroform), which by

* *Helv. Chim. Acta*, 1940, **23**, 288.

dehydrogenation with selenium afforded 6-ethylretene (CXVI), $C_{20}H_{22}$, m.p. $80-80.5^\circ$, trinitrobenzoate, m.p. $169.5-170.5^\circ$, also obtained by direct dehydrogenation of (CX).



When the oxime of methyl 6-acetyldehydroabietate was subjected to the Beckmann rearrangement a mixture of 6-methylamidocarboxydehydroabietic acid (CXVII), m.p. $254-255^\circ$, $[\alpha]_D^{25^\circ} + 82^\circ$ (in alcohol) (hydrolysed to 6-carboxydehydroabietic acid (CXVIII), m.p. above 280° , $[\alpha]_D^{25^\circ} + 71^\circ$ (in alcohol)), and of 6-aminodehydroabietic acid (CXIX), m.p. $214-215^\circ$, $[\alpha]_D^{25^\circ} + 82^\circ$ (in alcohol), acetyl derivative, m.p. $255-256^\circ$, $[\alpha]_D^{25^\circ} + 80^\circ$ (in alcohol) and its methyl ester (CXX), m.p. $137-137.5^\circ$, $[\alpha]_D^{25^\circ} + 81^\circ$ (in alcohol), hydrochloride, m.p. ca. 250° decomp., $[\alpha]_D^{25^\circ} + 61^\circ$ (in alcohol), acetyl derivative, $[\alpha]_D^{25^\circ} + 79^\circ$ (in alcohol), diacetyl

derivative, m.p. 150–151°, $[\alpha]_D^{25} + 75^\circ$ (in alcohol), was formed. By treatment with nitrous acid, the amino-ester (CXX) afforded *methyl 6-hydroxydehydroabietate* (CXXI), m.p. 157–157.5°, $[\alpha]_D^{25} + 71^\circ$ (in alcohol).*

When (CVI) was treated with bromine it afforded with great ease *6-bromodehydroabietic acid* (CXXII), m.p. 200–202°, $[\alpha]_D^{25} + 81^\circ$ (in alcohol), *methyl ester* (CXXIIa), m.p. 140.5–141°, $[\alpha]_D^{25} + 71^\circ$ (in acetone), which was also obtained directly by the action of bromine on dehydroabietic acid. By hydrolysis with sodium hydroxide and then esterification with diazomethane (CXXII) furnished *methyl 6-hydroxydehydroabietate* (CXXI). Similarly when (CXXII) was reacted under pressure with ammonia in the presence of cuprous bromide, *6-amino-dehydroabietic acid* (CXIX) was formed. These last two experiments prove the position of the bromine atom as in formula (CXXII) and therefore of the original sulphonic acid grouping in (CVI).†

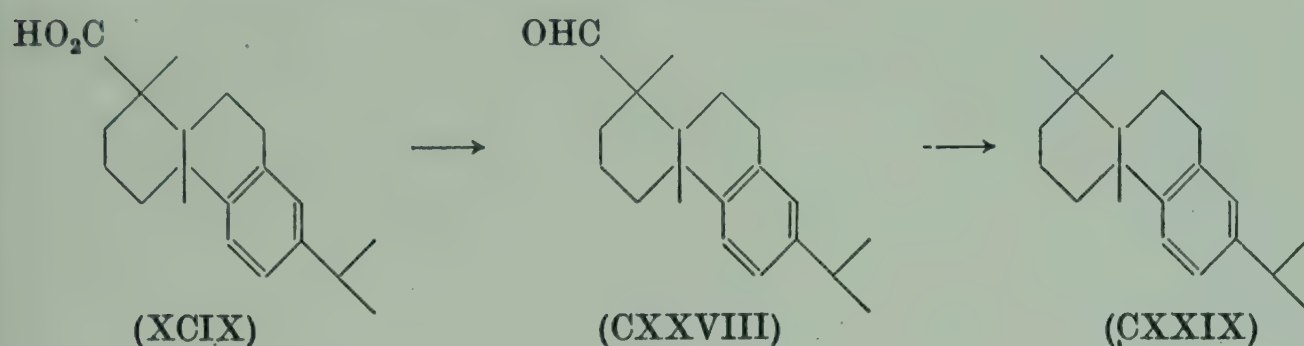
Campbell and Morgana‡ have also established with certainty the presence of one nitro group at the 6 position in the 6:8-dinitrodehydroabietic acid (C), previously mentioned on p. 413, and, therefore, made very probable the correctness of the 8 position for the other grouping. When *methyl 6:8-dinitrodehydroabietate* (Ca) was reduced with ammoniacal hydrogen sulphide, *methyl 8-nitro-6-aminodehydroabietate* (CXXIII), m.p. 239–242°, $[\alpha]_D^{25} + 105^\circ$ (in acetone), *diacetyl derivative*, m.p. 203.5–206°, $[\alpha]_D^{25} + 97^\circ$ (in acetone), was obtained. Using sodium sulphide in alcohol as the reducing agent, *8-nitro-6-aminodehydroabietic acid* (CXXIV), m.p. 285.5–286° decomp., $[\alpha]_D^{25} + 117^\circ$ (in acetone) resulted, which acid was also prepared by nitration of *6-aminodehydroabietic acid* (CXIX). Diazotisation of the ester (CXXIII) and reductive removal of the diazo group furnished *methyl 8-nitrodehydroabietate* (CXXV), m.p. 194–195°, $[\alpha]_D^{25} + 29^\circ$ (in acetone), which on nitration was converted back again to (Ca). The observation that (CVI) gives on nitration, besides the expected *8-nitrodehydroabietic acid 6-sulphonic acid* (CXXVI), m.p. above 300°, *dimethyl ester*, m.p. 244.3–244.7°, *diethyl ester*,

* Fieser and Campbell, *J. Amer. C.S.* 1939, **61**, 2528.

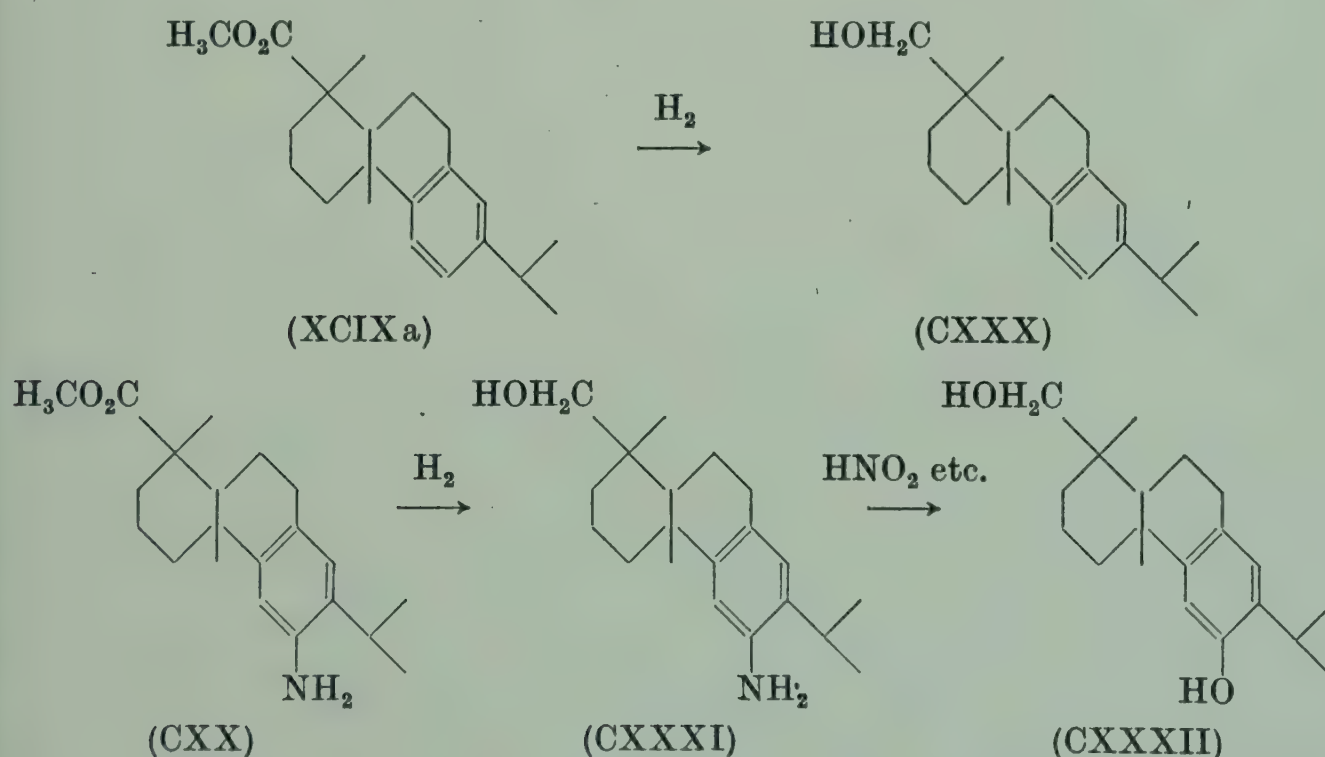
† Campbell and Morgana, *J. Amer. C.S.* 1941, **63**, 1838; compare p. 418.

‡ *Loc. cit.*

to *dehydroabietinal* (CXXVIII), the *semicarbazone*, m.p. 217–219°, of which by heating with sodium ethoxide afforded *dehydroabietane* (CXXIX), m.p. 41–44°.*



Methyl dehydroabietate (XCIXa), by high-pressure hydrogenation in the presence of copper chromite, was reduced to *dehydroabietinol* (CXXX), b.p. 177°/1 mm., $[\alpha]_D^{25} + 53^\circ$ (in alcohol), 3:5-dinitrobenzoate, m.p. 123–124°, whilst methyl 6-aminodehydroabietate (CXX) afforded similarly 6-amino-*dehydroabietinol* (CXXXI), m.p. 139.5–140°, $[\alpha]_D^{25} + 72^\circ$ (in alcohol), *hydrochloride*, $[\alpha]_D^{25} + 63^\circ$ (in alcohol), which gave on diazotisation and hydrolysis 6-*hydroxydehydroabietinol* (CXXXII), m.p. 180–181.5°, $[\alpha]_D^{25} + 72^\circ$ (in alcohol).†

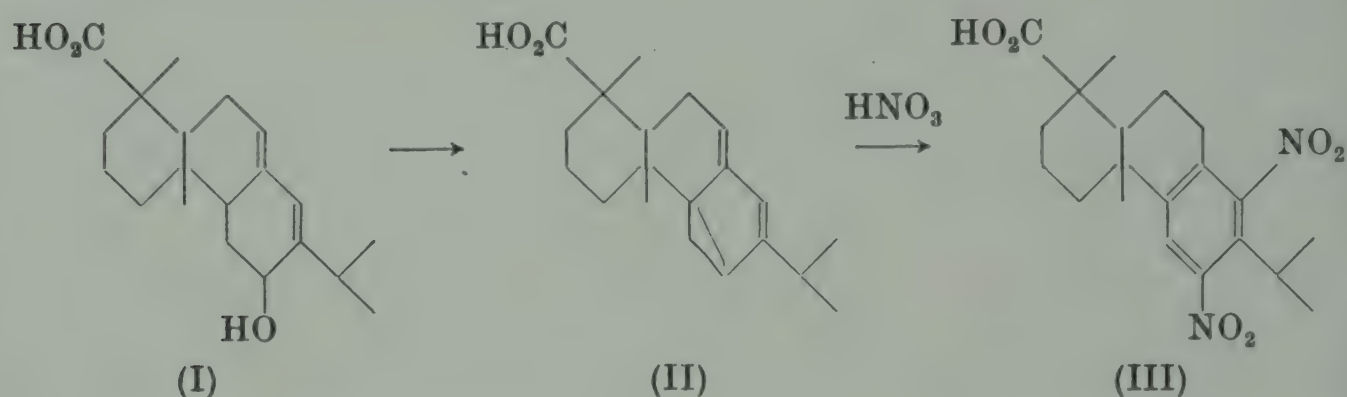


* Campbell and Todd, *J. Amer. C.S.* 1942, **64**, 928.

† Fieser and Campbell, *ibid.* 1939, **61**, 2528.

ISOABIETIC ACID

In 1938 Fieser and Campbell* observed that when 6-hydroxy-abietic acid (I) (see p. 412), or its quarter sodium salt, was heated at 175–200° in an atmosphere of nitrogen, dehydration occurred with the formation of an *acid*, m.p. 167.5–169.5°, $[\alpha]_D^{25} + 21^\circ$ (in alcohol), *methylester*, b.p. 174–178°/3 mm. This acid, $C_{20}H_{28}O_2$, was tentatively represented by (II), since it was oxidised with potassium permanganate to give *isobutyric acid* and was reduced by catalytic hydrogenation to a tetrahydroabietic acid, $C_{20}H_{34}O_2$, m.p. 164–164.5°, $[\alpha]_D^{25} + 26^\circ$ (in alcohol) (compare p. 384). Moreover, it was unsaturated towards bromine, afforded 6:8-dinitrodehydroabietic acid (III) (see p. 413) on nitration and had an ultra-violet absorption spectrum very similar to that of abietic acid (see p. 385).



The same acid, m.p. 172°, $[\alpha]_D + 21^\circ$, was said to have been prepared later by Sandermann† by the pyrolysis of the maleic anhydride adduct of levopimaric acid (IV) (see p. 431), and also by the action of potassium hydroxide an abietic acid dihydrobromide (V) (see p. 384). Sandermann suggested that the formula for this acid was $C_{20}H_{30}O_2$ and since it was thus isomeric with abietic acid he named it *isoabietic acid*.‡

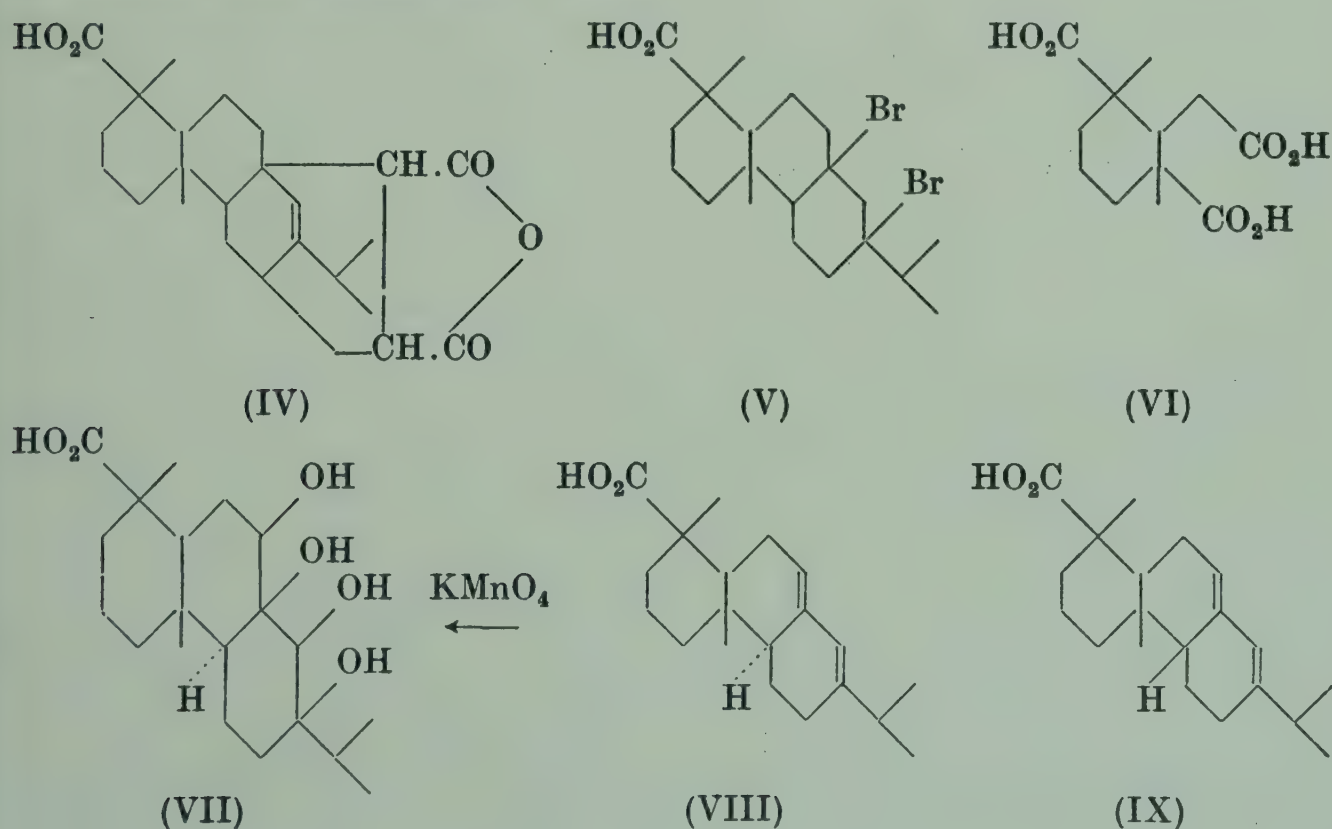
Whilst being able to confirm Fieser and Campbell's observations that *isoabietic acid* gave on nitration 6:8-dinitrodehydro-

* *J. Amer. C.S.* 1938, **60**, 159.

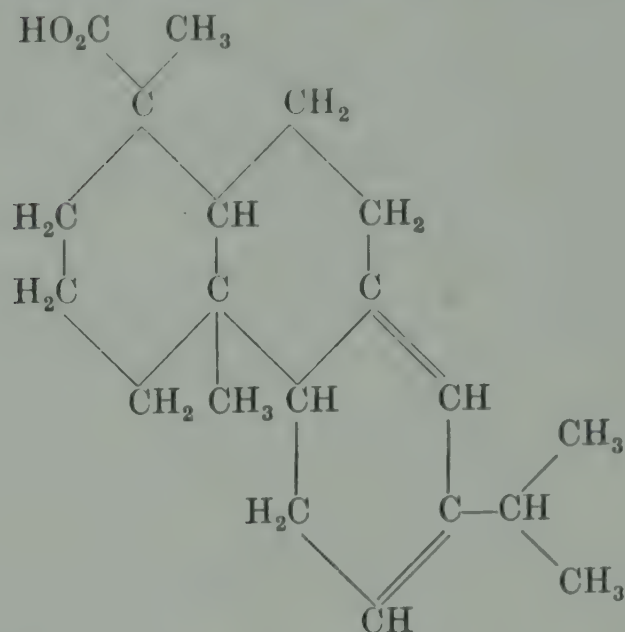
† *Ber.* 1943, **76**, 1257, 1261.

‡ It seems probable that this acid had been obtained earlier in an impure condition, by Hasselström and McPherson (*J. Amer. C.S.* 1939, **61**, 2247), by treating abietic acid dihydrobromide with sodium ethoxide, and it is possible that it had also been prepared in a similar state by Ruzicka and Meyer (*Helv. Chim. Acta*, 1922, **5**, 315) by the action of quinoline on the same dibromide. It is not improbable that this acid is present in abietic acid which has been distilled or sublimed.

abietic acid (III), and *isobutyric* acid on oxidation with potassium permanganate, Sandermann showed that in general it paralleled very closely in its reactions abietic acid. Thus it gave the same adduct with maleic anhydride and with diethyl acetylenedicarboxylate, and the same dihydrochloride and dihydrobromide by the action of the corresponding halogen acids. A further similarity was its oxidation by nitric acid to the tricarboxylic acid $C_{12}H_{18}O_6$ (VI) (see p. 387). By oxidation with potassium permanganate an amorphous *tetrahydroxyisoabietic acid*, $C_{20}H_{34}O_6$ (VII), was prepared which like α -tetrahydroxyabietic acid (p. 392) gave acetone on oxidation with chromic acid. On the basis of this evidence and because the absorption spectrum of *isoabietic* acid was identical with that of abietic acid, Sandermann suggested that these acids were stereoisomeric at C_{13} , as illustrated in the formulae (VIII) for *isoabietic* acid and (IX) for abietic acid. It is not certain, however, that *isoabietic* acid was really identical with the acid of Fieser and Campbell and its properties could possibly be explained if it were a mixture of abietic and neoabietic acids.



LEVOPIMARIC ACID



*Levopimaric acid** was first isolated in a state of purity by Vesterberg,[†] together with *d*-pimaric acid (see p. 447) from French galipot. Vesterberg ascribed to the acid the molecular formula $C_{20}H_{30}O_2$ and this was subsequently confirmed. Levopimaric acid is more soluble than *d*-pimaric acid, is easily autoxidised and rearranged to abietic acid (see p. 374) by the action of heat or in the presence of mineral acids. Its preparation therefore is far more difficult than that of *d*-pimaric acid or even of abietic acid. Köhler,[‡] utilising the oleo-resin of the red fir (*Picea excelsa*) collected in the winter, was able to confirm Vesterberg's characterisation of levopimaric acid and to show that it readily rearranged to abietic acid on heating, but it was not until Dupont[§] had described a reliable method for the preparation of the acid from French galipot that progress in the study of its difficult chemistry could be commenced. Dupont showed that it was essential in the preparation of this primary resin acid that temperatures should not exceed 60° , and that it should not be

* The names *d*-pimaric acid and *l*-pimaric acid were introduced by Vesterberg, the prefixes denoting the sign of their optical rotatory power. It has been decided here, in view of the fact that the two acids are not optical antipodes, to retain the designation *d*-pimaric acid for the dextrorotatory acid (see p. 447) and to use the name levopimaric acid for the laevorotatory isomer. This differentiation has the advantages of taking note of the true relationship of the two acids and, at the same time, of following the universally understood nomenclature which it might be confusing to alter.

[†] *Ber.* 1887, 20, 3248; compare Cailliot, *Bull. Soc. chim.* 1874 [ii], 21, 387.

[‡] *Arkiv. Kemi Min. Geol.* 1910, 4, No. 5, p. 29; *J. pr. Chem.* 1912 [ii], 85, 534.

[§] *Compt. rend.* 1921, 172, 923, 1184; *Bull. Soc. chim.* 1921 [iv], 29, 718; compare Ruzicka and Balas, *Helv. Chim. Acta*, 1923, 6, 677; Ruzicka, Balas and Vilim, *ibid.* 1924, 7, 458.

brought into contact with other acids, including even acetic acid. Exposure to direct sunlight greatly accelerated the rate of undesired autoxidation. Palkin and Harris* isolated pure levopimaric acid from the primary resin acids of *Pinus palustris* and *Pinus caribaea*, and it is now certain that levopimaric acid is a primary constituent of all resins from pine and fir trees, its presence therein being readily detected by its facile reaction with maleic anhydride or *p*-benzoquinone (see p. 436). It has also been shown that the so-called sapinic acids (see p. 379), formerly thought to be constituents of the primary oleoresin, all contain levopimaric acid.† Formerly the most convenient method of separating *d*-pimaric acid from levopimaric acid was fractionation of the mixed acids from a neutral solvent, conversion of the fractions enriched in levopimaric acid to the sodium salts and fractionation of these from water and, finally, reconversion to the acid and recrystallisation from a neutral solvent. During these operations the precautions suggested by Dupont had to be observed. Recently a greatly improved method of isolation has been reported by Harris and Sanderson.‡ In this procedure the levopimaric acid is concentrated as the crystalline *salt* with 2-amino-2-methylpropan-1-ol (butanolamine), $[\alpha]_D^{24} - 276^\circ$ (in alcohol), from which the pure acid is readily regenerated.

The facile isomerisation of levopimaric acid (I) to abietic acid (II) by the action of heat, by hot acetic acid or by treatment with mineral acid,§ indicated that the two acids probably had the same carbon skeleton. This received support from the observed dehydrogenation of the former acid with either sulphur or palladised charcoal to retene (III), which can also be prepared in this way from abietic acid (see p. 383).|| The dehydrogenation of both dihydro- and tetrahydro-levopimaric acids to the same hydrocarbon suggests that it is not an artefact formed during the reaction.¶

* *J. Amer. C.S.* 1933, **55**, 3677.

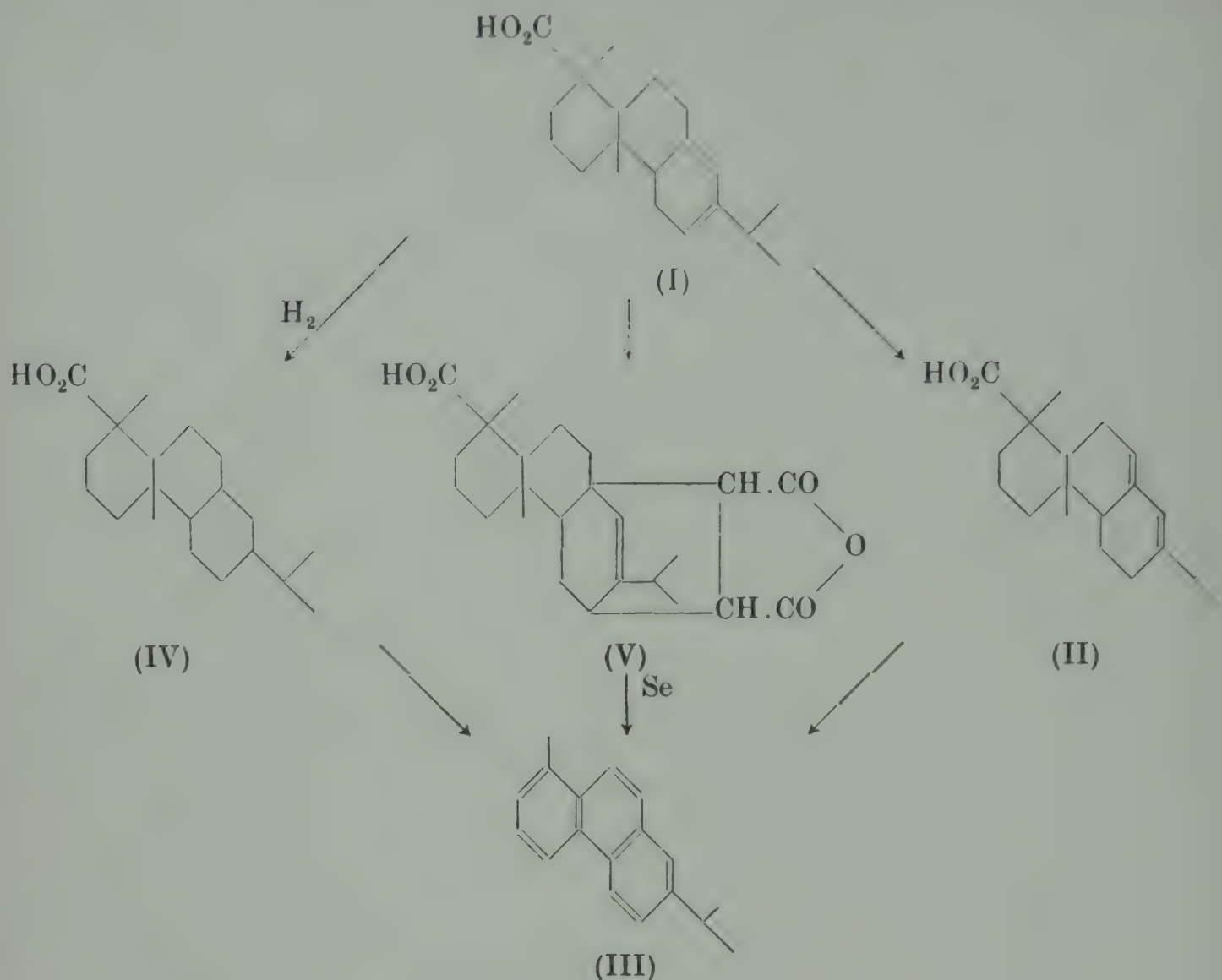
† Hasselström and Bogert, *J. Amer. C.S.* 1935, **57**, 2118; Kraft, *Annalen*, 1935, **520**, 133; 1936, **524**, 1; compare Vocke, *ibid.* 1933, **508**, 11; Sandermann, *Ber.* 1938, **71**, 2005; Arbusov, *Lesokhim. Prom.* 1940, **3**, No. 5, p. 3.

‡ *J. Amer. C.S.* 1948, **70**, 334.

§ *Inter al.* Köhler, *loc. cit.*; Dupont, *Compt. rend.* 1921, **172**, 923, 1373; *Bull. Soc. chim.* 1921 [iv], **29**, 718, 727; Ruzicka, Balas and Vilim, *Helv. Chim. Acta*, 1924, **7**, 458; Lombard, *Bull. Soc. chim.* 1948 [v], **15**, 1186. The kinetics of this reaction have been studied by Ritchie and McBurny, *J. Amer. C.S.* 1949, **71**, 3736.

|| Ruzicka, Balas and Vilim, *loc. cit.*; Sandermann, *Ber.* 1941, **74**, 154.

¶ Ruzicka and Bacon, *Helv. Chim. Acta*, 1937, **20**, 1542.



The presence of two double bonds in levopimaric acid, and therefore of three rings as implied by the above observations, has been proved by the hydrogenation of the acid to a saturated *tetrahydrolevopimaric acid*, $C_{20}H_{34}O_2$ (IV), m.p. 195–197°, $[\alpha]_D + 7^\circ$ (in alcohol), methyl ester, m.p. 76–77°, $d_4^{91^\circ} 0.9705$, $n_D^{91^\circ} 1.4844$, $[\alpha]_D + 3^\circ$ (in alcohol),* using a platinum catalyst in acetic acid solution.† The presence of two double bonds in levopimaric acid has been confirmed by Kraft‡ by titration with perbenzoic acid and is supported by the molecular refractions of the methyl and ethyl levopimarates and of methyl dihydro- and tetrahydrolevopimarates (see pp. 436, 437).

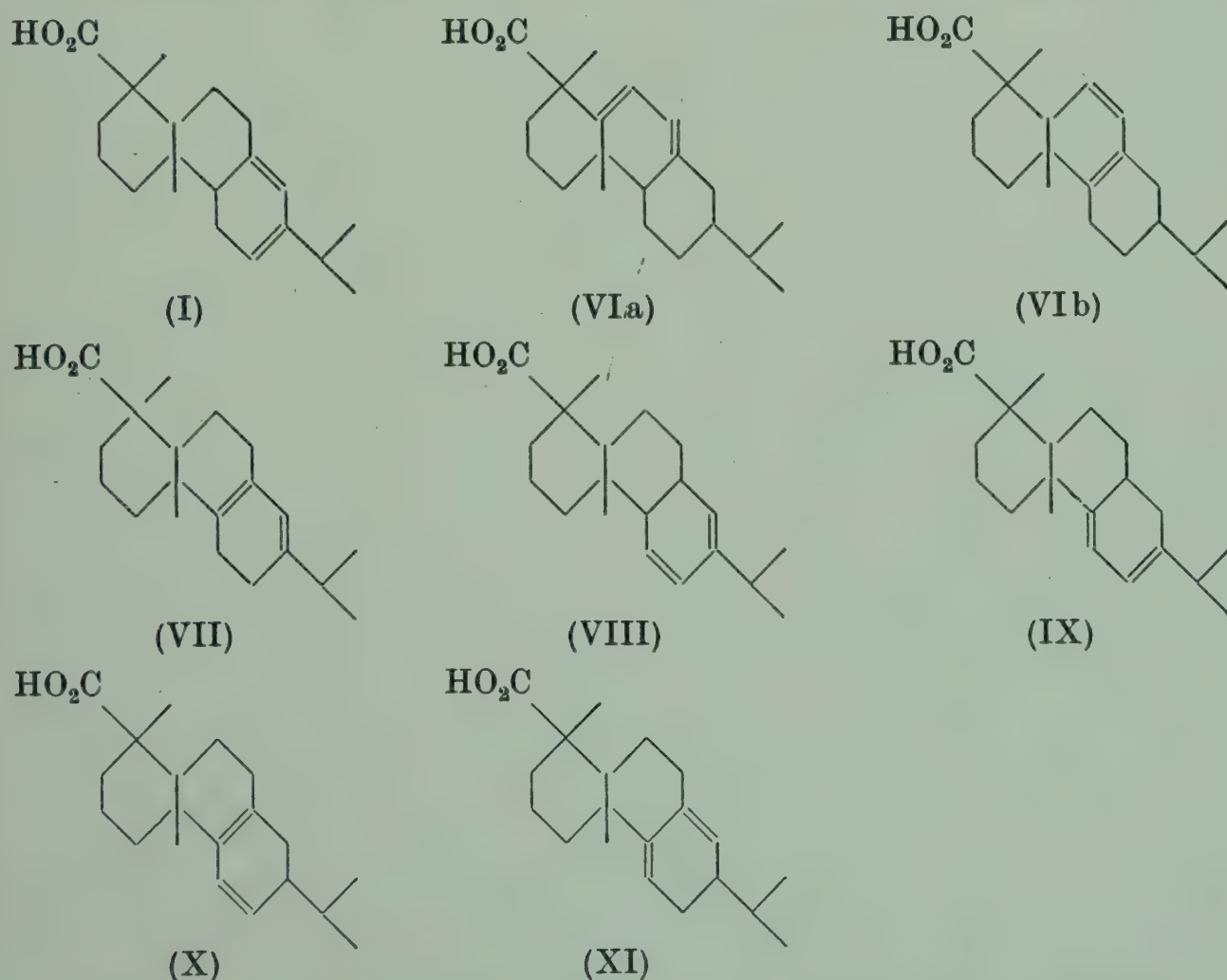
* A tetrahydrolevopimaric acid, having somewhat different constants, m.p. 144–148°, $[\alpha]_D + 14^\circ$ (in alcohol), raised to 156–158° on further crystallisation, was obtained by Ruzicka, Balas and Vilim (*Helv. Chim. Acta*, 1924, 7, 458), by hydrogenation of levopimaric acid using a platinum catalyst in ethyl acetate solution at 50°.

† Ruzicka and Bacon, *Chem. and Ind.* 1936, p. 546; *Helv. Chim. Acta*, 1937, 20, 1542.

‡ *Annalen*, 1936, 524, 1.

In addition, the two double bonds of levopimaric acid must be in conjugation for it reacts quantitatively in benzene solution at room temperature with maleic anhydride to afford the same *adduct*, $C_{24}H_{32}O_5$ (V), m.p. 226–227°, $[\alpha]_D - 29.6^\circ$ (in chloroform), -28.9° (in methyl alcohol), *methyl ester* (Va), m.p. 214–215°,* as is obtained from abietic acid under more vigorous conditions (see p. 385).† This adduct, as might be expected, furnished retene on dehydrogenation with selenium.‡ Since levopimaric acid shows an absorption maximum in the ultra-violet at 272.5 m μ with $\log \epsilon = 3.9$,§ it follows that these two conjugated double bonds must be contained in one ring, as indeed would be expected from the ease of addition of maleic anhydride.

On the basis of the above considerations the only possible representations for levopimaric acid are (I) and (VI) to (XI). Formulae (VIa) and (VIb) are most unlikely since levopimaric

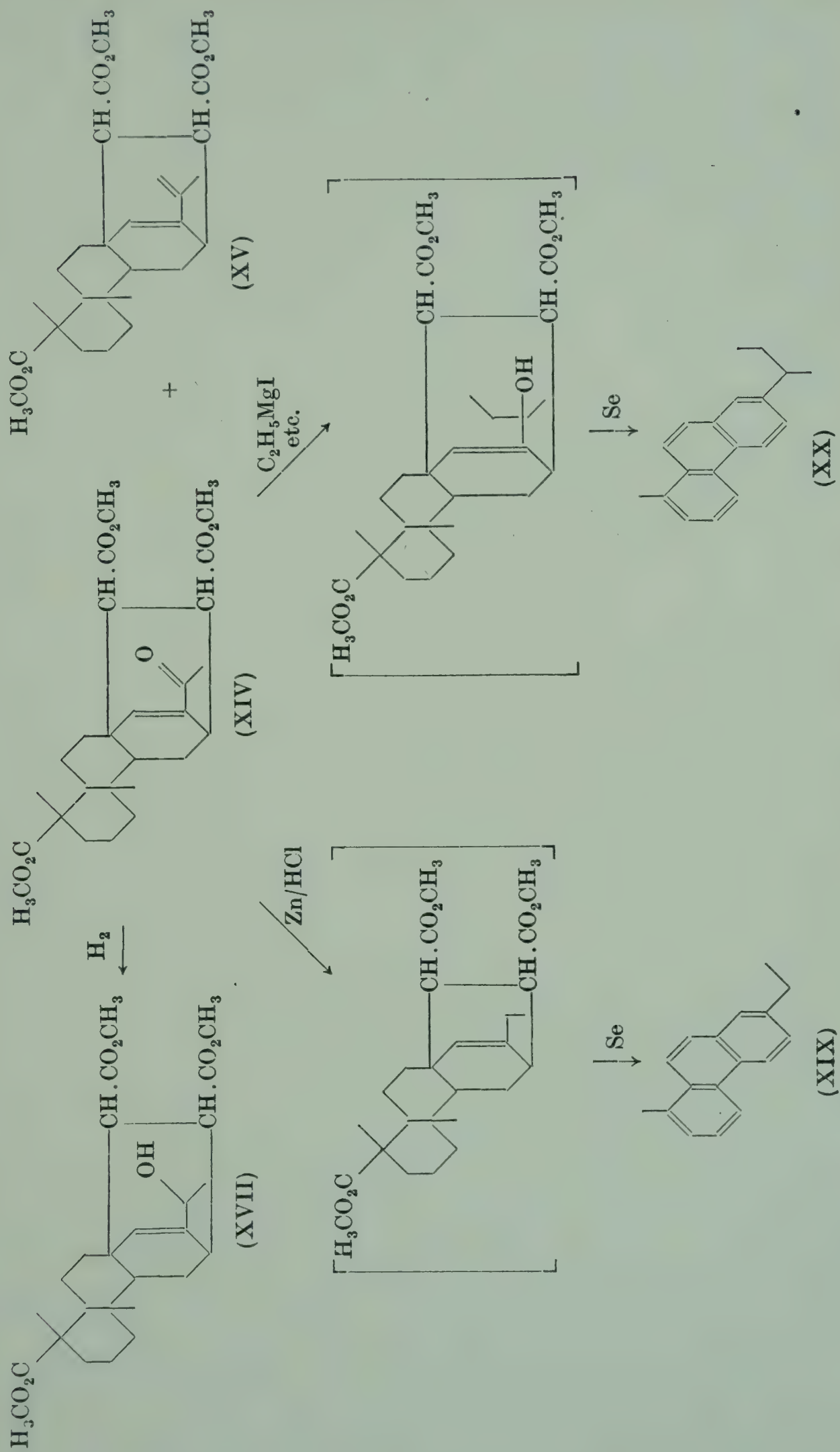


* According to Graaff (*J. Amer. C.S.* 1946, **68**, 1937) this ester has m.p. 228–230°, $[\alpha]_D - 26^\circ$ (in chloroform).

† Arbusov, *J. Gen. Chem. U.S.S.R.* 1932, **2**, 806; Ruzicka, Ankersmit and Frank, *Helv. Chim. Acta*, 1932, **15**, 1289; Ruzicka and Bacon, *ibid.* 1937, **20**, 1542; Wienhaus and Sandermann, *Ber.* 1936, **69**, 2202.

‡ Arbusov, *loc. cit.*

§ Kraft, *Annalen*, 1935, **520**, 138.



acid affords isobutyric acid on ozonolysis (compare abietic acid, p. 386)* and, of the remainder, all but two, (I) and (VIII), can be dismissed as a result of the elegant experiments of Ruzicka and Kaufmann,† which must now be discussed.

When the methyl ester (Va) of the maleic anhydride adduct of levopimaric acid was hydrated it afforded a *dicarboxylic acid* (XII), *trimethyl ester* (XIII), m.p. 103°, $d_4^{16^\circ}$ 1.084, $n_D^{14.8^\circ}$ 1.4869, $n_D^{149.6^\circ}$ 1.4760.‡ This trimethyl ester on ozonolysis furnished the *trimethyl ester* of a monounsaturated *keto-tricarboxylic acid*, $C_{26}H_{36}O_7$ (XIV), m.p. 168–169°, *oxime*, m.p. 174–176°, and the *trimethyl ester* of a diunsaturated *tricarboxylic acid*, $C_{27}H_{38}O_6$ (XV) m.p. 124–126° (λ max. 240 m μ with $\log \epsilon = 4.25$). This latter ester regenerated the original trimethyl ester (XIII) on catalytic hydrogenation. The absorption spectrum, with λ max. 240 m μ and $\log \epsilon = 4.25$, showed the keto-trimethyl ester (XIV) to be an $\alpha:\beta$ -unsaturated ketone. It was hydrolysed and oxidised by alkaline sodium hypobromite solution to the *monomethyl ester* of a *tetracarboxylic acid*, $C_{23}H_{30}O_8$ (XVI), m.p. 280–283°, *tetramethyl ester*, m.p. 152–153°, one of whose carboxylic acid groups was in the $\alpha:\beta$ -position with respect to the ethylenic linkage as shown by the absorption maximum of its tetramethyl ester at 227 m μ with $\log \epsilon = 4.18$. The keto-trimethyl ester (XIV) was partially hydrolysed by methanolic potassium hydroxide to a *dimethyl ester*, $C_{25}H_{34}O_7$, (XVIIIa) or (XVIIIb), m.p. 226–228°, whilst it was catalytically hydrogenated with a platinum catalyst in acetic acid solution to the corresponding secondary *alcohol*, $C_{26}H_{38}O_7$ (XVII), m.p. 128–129°. Reduction of the ester (XIV) by the Clemmensen method and dehydrogenation of the product with selenium gave 1-methyl-7-ethylphenanthrene (XIX), m.p. 62.5–63°, *trinitrobenzoate*, m.p. 132–133°, whilst by treatment with ethyl magnesium iodide prior to dehydrogenation 1-methyl-7-sec.butylphenanthrene (XX), m.p. 87.5°, *trinitrobenzoate*, m.p. 134°, was obtained. The structure of both of these hydrocarbons was proved by comparison with synthetic specimens and their formation proves with certainty that the double bond of the adduct (Va) must be adjacent to the isopropyl grouping. Only

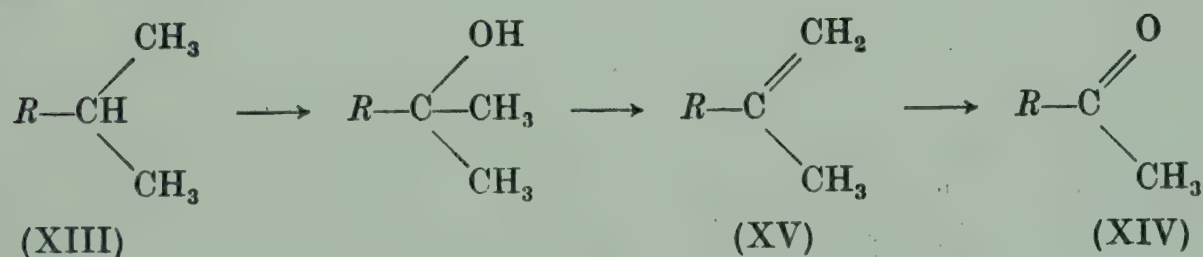
* Ruzicka, Bacon, Lukes and Rose, *Helv. Chim. Acta*, 1938, **21**, 583; Malevskaja, *J. Appl. Chem. U.S.S.R.* 1940, **13**, 1085.

† *Helv. Chim. Acta*, 1940, **23**, 1346; 1941, **24**, 939.

‡ Compare Ruzicka, Ankersmit and Frank, *ibid.* 1932, **15**, 1289.

the formulae (I) and (VIII), therefore, are possible representations of *levopimaric acid*. Evidence in favour of (I), which in any case explains the ease of rearrangement of *levopimaric acid* to *abietic acid* more satisfactorily than (VIII), has been obtained by Arbusov.* As mentioned in detail later (p. 436) *levopimaric acid* and α -naphthaquinone furnish an adduct. When this was dehydrogenated by aerial oxidation of the alcoholic alkaline solution and the product pyrolysed and then oxidised further with nitric acid anthraquinone-1:3-dicarboxylic acid was formed. According to Arbusov this is a proof of the correctness of formula (I). Sandermann† has also advanced theoretical evidence in support of this structure for *levopimaric acid*.

It will have been observed that in the ozonolysis of the unsaturated trimethyl ester (XIII) the ethylene linkage is not attacked, but instead degradation of the *isopropyl* side chain occurs. Whereas the resistance of double bonds to the action of ozone has been frequently noted,‡ so far as we are aware there is no analogy to the oxidation of an *isopropyl* group with this reagent. The reaction proceeds formally by the primary formation of a tertiary alcohol which, by loss of water, changes to the corresponding *isopropenyl* compound. Indeed this *isopropenyl* compound (XV) was found to be present amongst the products of the ozonolysis. The formation of (XIV) and (XV) can be represented, therefore, by the following scheme ($R = C_{23}H_{31}O_6$):



In view of the relationship between *levopimaric acid* and *abietic acid*, rings A and C of the latter must likewise be fused in the *trans* sense (see p. 405).

* *Bull. Acad. Sci. U.R.S.S., Cl. Sci. Chim.* 1940, p. 95; *Compt. Rend. Acad. Sci. U.R.S.S.* 1941, **30**, 723; *Chem. Zent.* 1942, **II**, 892, 893.

† *Ber.* 1941, **74**, 154; Sandermann and Holm, *ibid.* 1943, **76**, 1257; compare Ruzicka and Kaufmann, *Helv. Chim. Acta*, 1941, **24**, 1425.

‡ Eccott and Linstead, *J.C.S.* 1930, p. 914; Penfold, Ramage and Simonsen, *ibid.* 1939, p. 1499.

The melting-point, *ca.* 150° , of levopimaric acid is not sharp, due to isomerisation of the acid near the melting-point and is not, therefore, of much value as a criterion of purity. The determination of the optical rotatory power is a more satisfactory criterion of the purity of the acid. For the pure acid $[\alpha]_D$ is *ca.* -280° (in alcohol), *ca.* -265° (in chloroform) and $[\alpha]_J$ is *ca.* -291° (in alcohol), *ca.* -273° (in chloroform).^{*} Levopimaric acid forms a *methyl ester* (Ia), m.p. $63-64^{\circ}$, d_4^{78} 0.9981, n_D^{65} 1.5083, n_D^{72} 1.5074, $[\alpha]_D$ -268° (in ether) and an *ethyl ester*, b.p. $175-177^{\circ}/0.5$ mm., d_4^{23} 1.0124, n_D^{23} 1.5153, $[\alpha]_D$ -170.9° (in alcohol), which was probably partly isomerised at the temperature required for distillation, has also been described.[†] Levopimaric acid is, however, best identified by the preparation of its adduct with maleic anhydride (see p. 431).[‡] This, on alkaline hydrolysis, gives the corresponding *tricarboxylic acid* (XXI), m.p. $227-228^{\circ}$, $[\alpha]_D$ -25° (in chloroform).[§] It also reacts with great ease with *p*-benzoquinone to give the corresponding *adduct* (XXII), $C_{26}H_{34}O_4$, m.p. 192° , $[\alpha]_D$ -163° (in chloroform), λ max. 230, 295 and $380 m\mu$ with $\log \epsilon = 4.2, 2.9$ and 2.2 respectively^{||}; with α -naphthaquinone to give the *adduct* (XXIII), $C_{30}H_{36}O_4$, m.p. 185° , *methyl ester*, m.p. 195° ,[¶] and with β -naphthaquinone to give the isomeric *adduct*, (XXIV a) or (XXIV b), $C_{30}H_{36}O_4$, m.p. $202-203^{\circ}$, *quinoxaline* derivative, m.p. $176-177^{\circ}$.^{**} Dimethyl acetylenedicarboxylate also reacts with levopimaric acid to give an *adduct*,

* Köhler, *Arkiv. Kemi. Min. Geol.* 1910, **4**, No. 5, p. 29; *J. Pr. Chem.* 1912 [ii], **85**, 534; Dupont, *Bull. Soc. chim.* 1921 [iv], **29**, 718; Ruzicka, Balas and Vilim, *Helv. Chim. Acta*, 1924, **7**, 458; Balas, *Casopis Cesk. Lekarnictva*, 1927, **7**, 320; Palkin and Harris, *J. Amer. C.S.* 1933, **55**, 3677; compare Vesterberg, *Ber.* 1887, **20**, 3248.

† Ruzicka, Balas and Vilim, *loc. cit.*; Ruzicka and Bacon, *Chem. and Ind.* 1936, p. 546; *Helv. Chim. Acta*, 1937, **20**, 1542.

‡ For the quantitative determination of levopimaric acid in mixtures of resin acids see *inter al.* Sandermann, *Bull. Inst. Pin.* 1937, p. 137; *Seifensieder Ztg.* 1937, **64**, 402, 421; *Ber.* 1938, **71**, 2005; *Fette und Seife*, 1942, **49**, 578; Fleck and Palkin, *Ind. Eng. Chem., Anal. Ed.*, 1942, **14**, 146; Davis and Fleck, *Ind. Eng. Chem.* 1943, **35**, 171; Komshilov, *Lesokhim. Prom.* 1940, No. 9, p. 10.

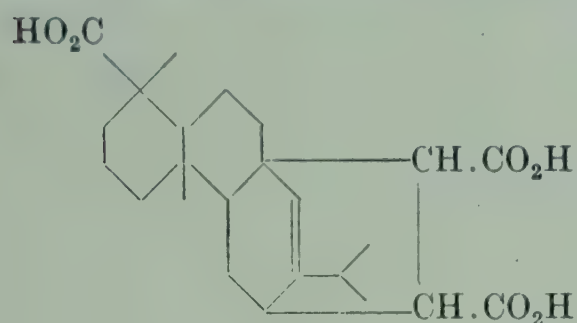
§ Compare Ruzicka, Ankersmit and Frank, *Helv. Chim. Acta*, 1932, **15**, 1289; for other simple derivatives of the maleic anhydride adduct see above.

|| Ruzicka and Kaufmann, *Helv. Chim. Acta*, 1941, **24**, 1425; compare Wienhaus and Sandermann, *Ber.* 1936, **69**, 2204; Malevskaja, *J. Appl. Chem. U.S.S.R.* 1940, **13**, 1085; Sandermann, *Ber.* 1941, **74**, 154.

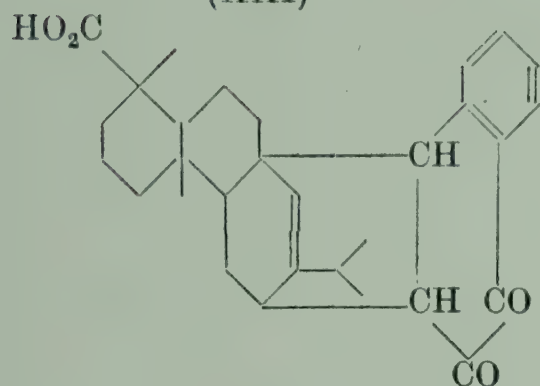
¶ Wienhaus and Sandermann, *loc. cit.*; compare Arbusov, *Bull. Acad. Sci. U.R.S.S.* 1940, p. 95.

** Arbusov, *Compt. Rend. Acad. Sci. U.R.S.S.* 1941, **30**, 718; *J. Gen. Chem. U.S.S.R.* 1942, **12**, 343.

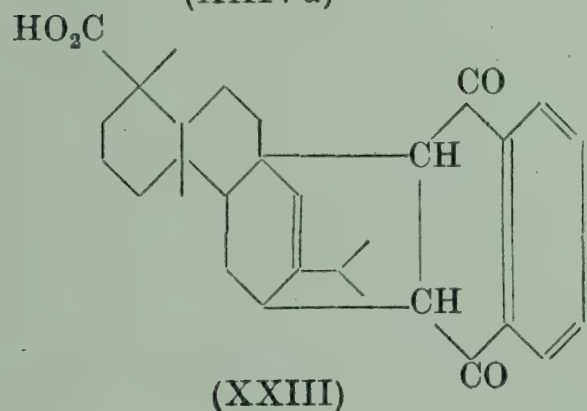
which by alkaline hydrolysis affords the corresponding *tricarboxylic acid*, $C_{24}H_{32}O_6$ (XXV), m.p. 169–170°.*



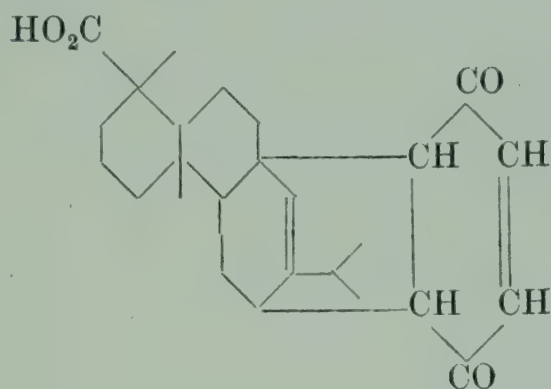
(XXI)



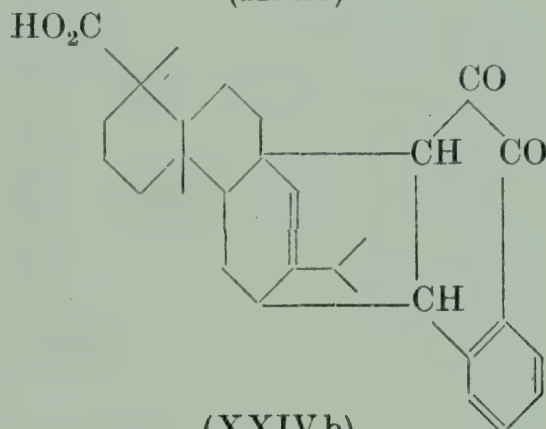
(XXIV a)



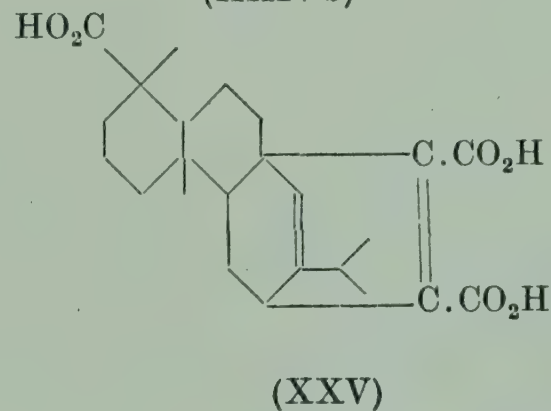
(XXIII)



(XXII)



(XXIV b)



(XXV)

Like abietic acid (see p. 407), levopimaric acid can be partially hydrogenated to give dihydro-acids, the reactivity of one double bond being appreciably greater than that of the other. By reduction in neutral solvents using a platinum catalyst Ruzicka and Bacon[†] prepared a *dihydrolevopimaric acid*, $C_{20}H_{32}O_2$, m.p. 135–136°, $[\alpha]_D + 35^\circ$ (in alcohol), *methyl ester*, m.p. 88°, $d_4^{111^\circ} 0.9593$, $d_4^{102^\circ} 0.9645$, $n_D^{102^\circ} 1.4841$, which with perphthalic acid afforded an *oxidodihydrolevopimaric acid*, $C_{20}H_{32}O_3$, m.p. 133–135°, $[\alpha]_D - 16.5^\circ$ (in alcohol).[‡] The structure of this acid has

* Sandermann and Höhn, *Ber.* 1943, **76**, 1257.

[†] *Chem. and Ind.* 1936, p. 546; *Helv. Chim. Acta*, 1937, **20**, 1542; compare Ruzicka, Balas and Vilim, *ibid.* 1924, **7**, 458; Palkin and Harris, *J. Amer. C.S.* 1933, **55**, 3677.

[‡] Ruzicka and Kaufmann, *Helv. Chim. Acta*, 1941, **24**, 1425.

not been determined and, like the various dihydroabiatic acids (see pp. 407–9), it may be a mixture resistant to separation by crystallisation. Fleck and Palkin* showed that the lactone of hydroxytetrahydroabiatic acid (see p. 410) was formed when this dihydrolevopimaric acid was treated with cold concentrated sulphuric acid, and the formation of this lactone has been applied as a test by Fleck and Palkin† to demonstrate the presence of a dihydrolevopimaric acid, not necessarily identical with that described above, in the oleoresins and resins of *Pinus palustris* and *Pinus caribaea*.

The oxidation of levopimaric acid leads to a complex mixture of products, the examination of which has been a matter of considerable difficulty. A careful study of the oxidation of the acid with potassium permanganate has been made by Ruzicka, Bacon, Lukes and Rose‡ and by Ruzicka and Kaufmann.§ Using two equivalents of the oxidising agent two ill-defined *dihydroxy-levopimaric acids*, $C_{20}H_{32}O_4$, m.p. ca. 206–207° and m.p. ca. 194–196°, *methyl ester*, m.p. 138·5–140°, $[\alpha]_D - 35\cdot3^\circ$ (in alcohol), were obtained. Oxidation of the amorphous residue remaining after the removal of these acids with a further two equivalents of potassium permanganate gave an *acid*, $C_{20}H_{32}O_5$, m.p. ca. 210°, *methyl ester*, m.p. 174–176°, whilst by esterification of this residue with diazomethane the *methyl ester* of an isomeric *hydroxy acid*, $C_{21}H_{34}O_5$, m.p. 183°, b.p. 300°/12 mm., $[\alpha]_D + 13\cdot5^\circ$ (in methyl alcohol) (*monoacetyl* derivative m.p. 124°), was isolated. This latter methyl ester had been prepared previously by Wienhaus and Sandermann|| and had been formulated as the methyl ester of an *oxidodihydroxylevopimaric acid* (XXVI).¶ Wienhaus and Sandermann found that this ester gave *methyl oxidochlorohydroxylevopimarate*, $C_{21}H_{33}O_4Cl$ (XXVII), m.p. 167°, when treated with hydrogen chloride, and, under more drastic conditions, with the same reagent, a *methyl trichlorohydroxylevopimarate*, $C_{21}H_{33}O_3Cl_3$ (XXVIII), m.p. 145–147°, the formation of both these substances being in agreement with the formula (XXVI) for the parent compound. The methyl ester (XXVI) is isomerised by digestion with sulphuric acid to an *ester*, m.p. 201°,

* *J. Amer. C.S.* 1939, **61**, 3197.

‡ *Helv. Chim. Acta*, 1938, **21**, 583.

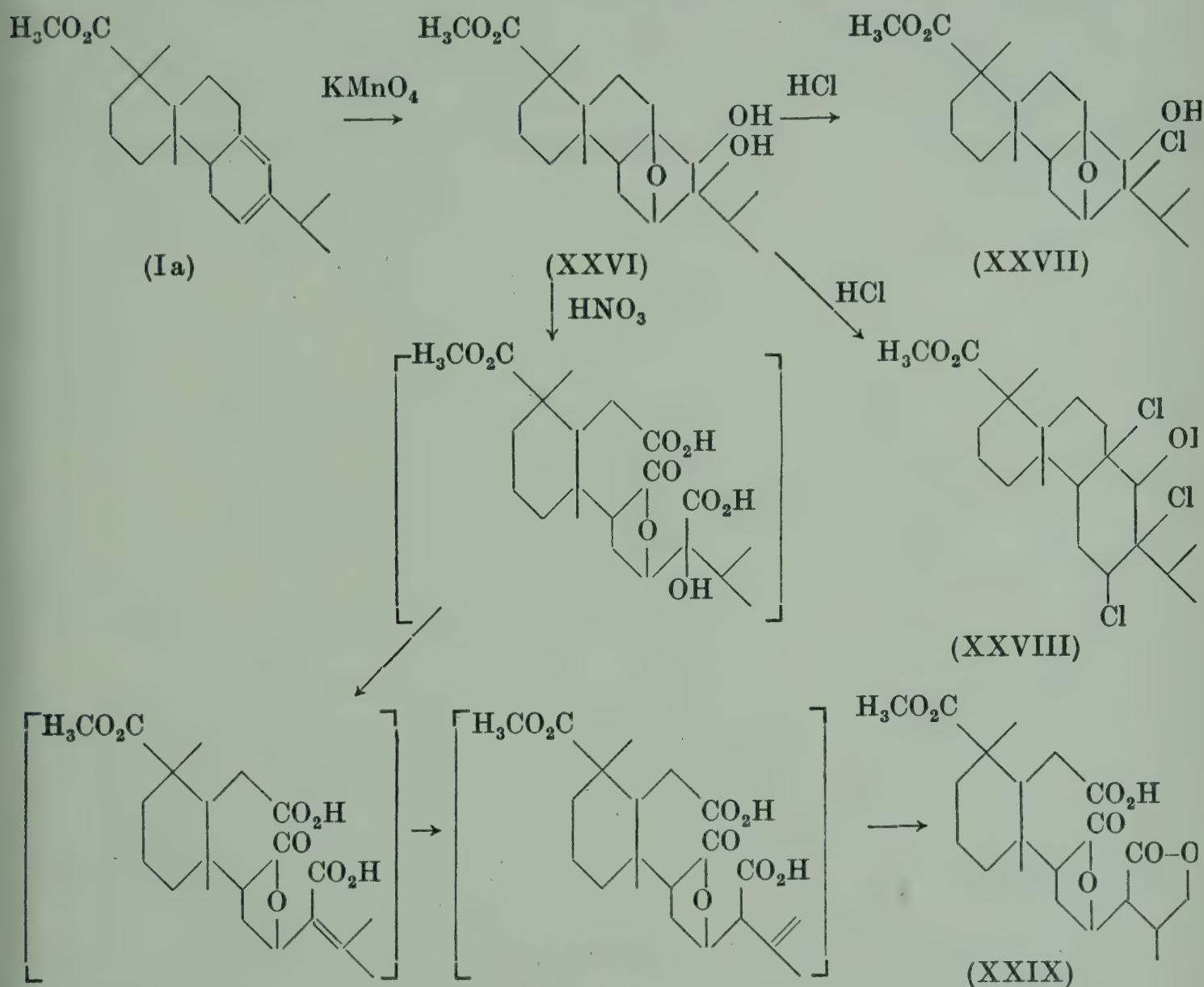
|| *Ber.* 1938, **71**, 1094.

¶ See Sandermann, *Ber.* 1941, **74**, 154.

† *Ibid.* 1939, **61**, 1230.

§ *Ibid.* 1941, **24**, 1425.

of unknown constitution, whilst on further oxidation with nitric acid it afforded a *monocarboxylic acid*, $C_{21}H_{30}O_8$, m.p. ca. 245° decomp., which has been formulated by Sandermann* as (XXIX). A third *dihydroxylevopimaric acid*, $C_{20}H_{32}O_4$, m.p. 243° , resulting presumably from levopimaric acid, was obtained



by Wienhaus and Sandermann by potassium permanganate oxidation of a specimen of primary resin acids, but the relationships of this substance to the isomeric dihydroxy-acids mentioned above is still undetermined.

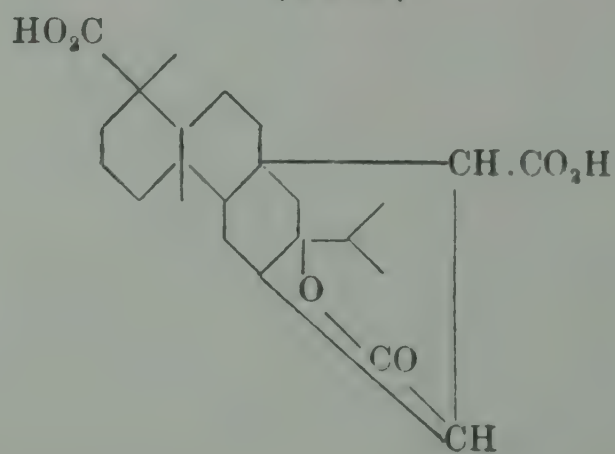
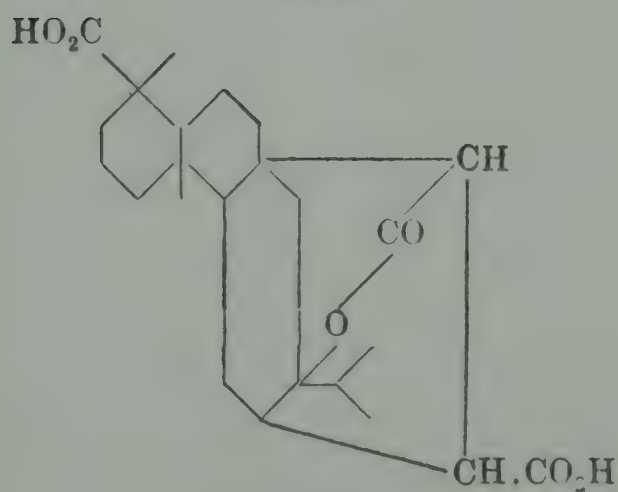
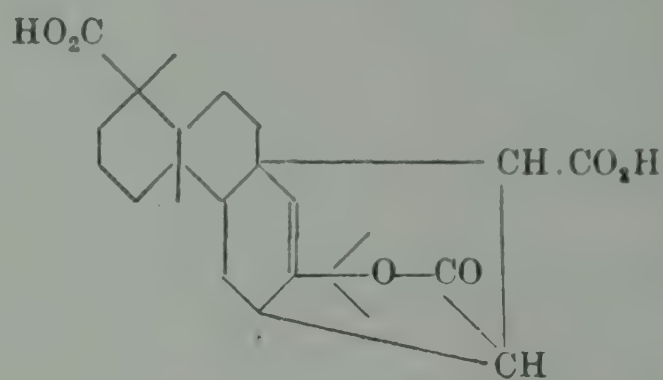
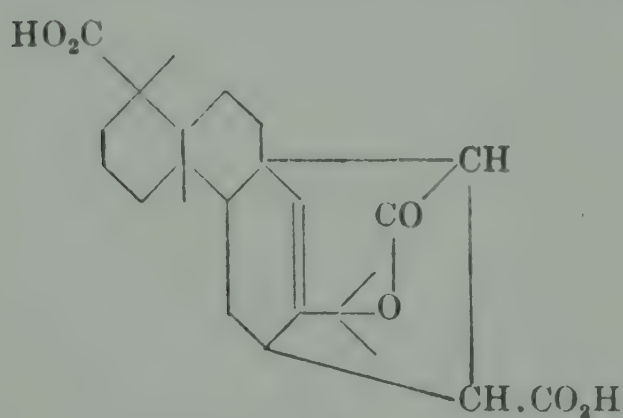
The oxidation by potassium permanganate of the adduct of levopimaric acid with maleic anhydride (V) has been studied by Arbusov[†] and by Ruzicka and Lalande.[‡] Arbusov isolated a substance, $C_{24}H_{34}O_7$, m.p. $191-192^\circ$, which he considered was

* *Loc. cit.*

[†] *J. Gen. Chem. U.S.S.R.* 1932, 2, 806.

[‡] *Helv. Chim. Acta*, 1940, 23, 1357; compare Arbusov, *Compt. Rend. Acad. Sci. U.R.S.S.* 1941, 30, 718; *J. Gen. Chem. U.S.S.R.* 1942, 12, 343.

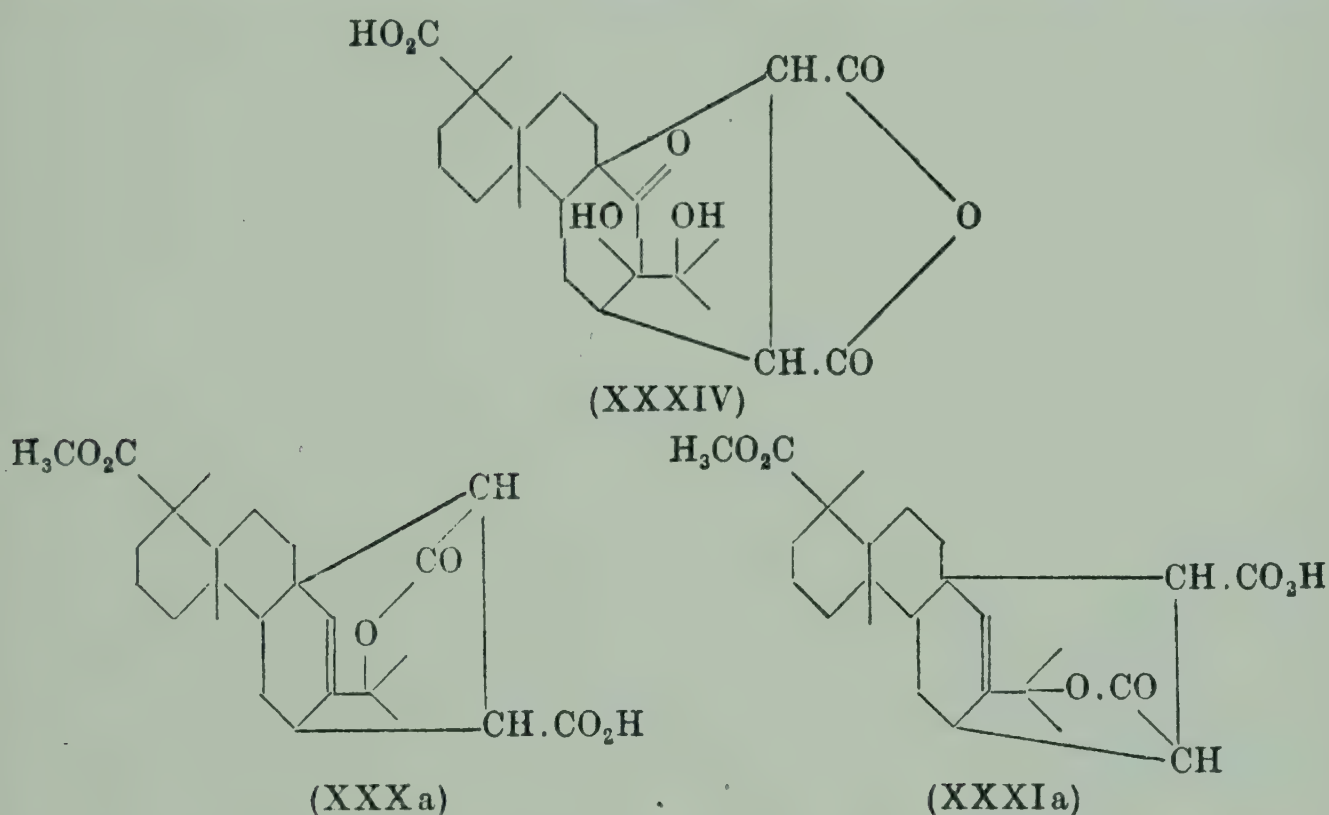
probably a δ -lactone, but its structure is still unknown and its formation has not been confirmed. Ruzicka and Lalande, using one equivalent of the oxidising agent, obtained two *lactonic dicarboxylic acids*, $C_{24}H_{32}O_6$, m.p. $211-212^\circ$, *dimethyl ester*, m.p. $182-184^\circ$, and $C_{24}H_{34}O_6$, m.p. $250-252^\circ$, *dimethyl ester*, m.p. $218-220^\circ$. The first of these compounds was formulated as (XXX) or (XXXI) and the second as the lactone formed by simple intramolecular addition of one of the carboxyl groups of the adduct to the double bond (XXXII) or (XXXIII). Using two equivalents of potassium permanganate, Ruzicka and Lalande obtained exclusively the acid (XXX) or (XXXI), whilst



by a similar oxidation of (XXX) or (XXXI) with three equivalents of the oxidising agent, a *monocarboxylic acid*, $C_{24}H_{32}O_8$, m.p. $307-308^\circ$ decomp., *diacetyl derivative*, m.p. $273-275^\circ$, *methyl ester*, m.p. $276-278^\circ$, resulted. For this latter acid Ruzicka and Lalande tentatively suggest the formula (XXXIV), but no functional derivatives of the carbonyl group have been prepared.

When the maleic anhydride adduct (Va), of methyl levopimarate is subjected to ozonolysis a *methyl ester*, $C_{25}H_{34}O_8$, m.p.

ca. 250°, is obtained.* Ruzicka and Lalande† have carefully examined the reaction products of this ozonolysis and found that two other substances are formed in addition. These compounds were *monomethyl esters* of two isomeric *dicarboxylic acids*, $C_{25}H_{34}O_6$, m.p. 289–290° and m.p. 226–227° (*dimethyl ester*, m.p. 182–183°) respectively, and the dimethyl ester of the latter acid was identical with the dimethyl ester of the substance formulated above as (XXX) or (XXXI). As the reactions of the two compounds were completely parallel Ruzicka and Lalande considered one to be represented by (XXXa) and the other by (XXXIa), but they were unable to assign distinct formulae. Ruzicka,

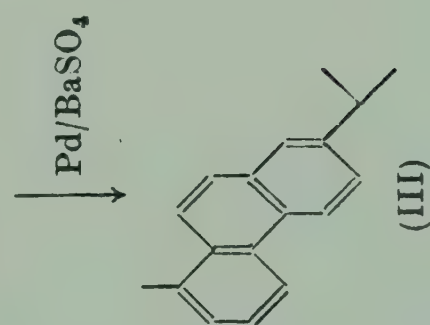
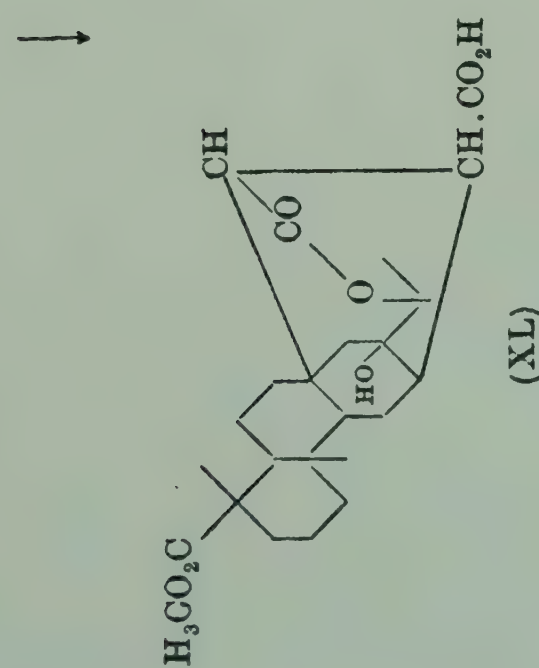
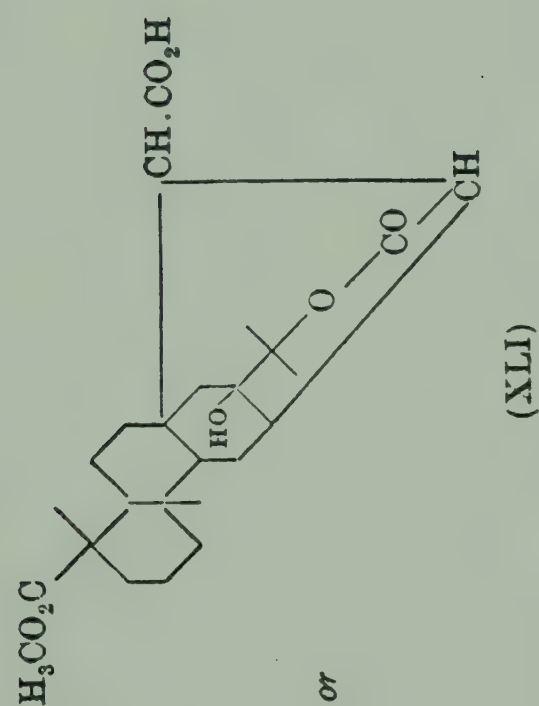
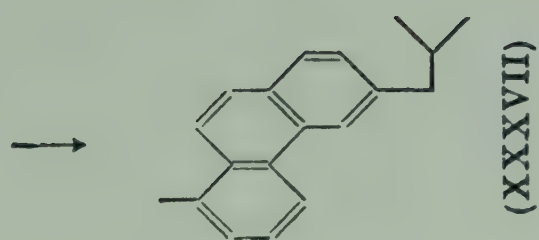


Bacon, Lukes and Rose‡ suggested tentatively that the monomethyl ester, $C_{25}H_{34}O_8$, m.p. *ca.* 250°, of Wienhaus and Sandermann (see above) might be represented by (XXXV). On reduction by the Clemmensen method a *dicarboxylic acid*, $C_{24}H_{34}O_7$, m.p. 295°, *dimethyl ester*, m.p. 200°, was obtained which, on the basis of formulae (XXXV) for the starting material, would be (XXXVI). However, on dehydrogenation with palladised barium sulphate, the expected 1-methyl-6-isobutyl-phenanthrene (XXXVII) was not obtained, but instead a hydrocarbon which was probably retene (III).

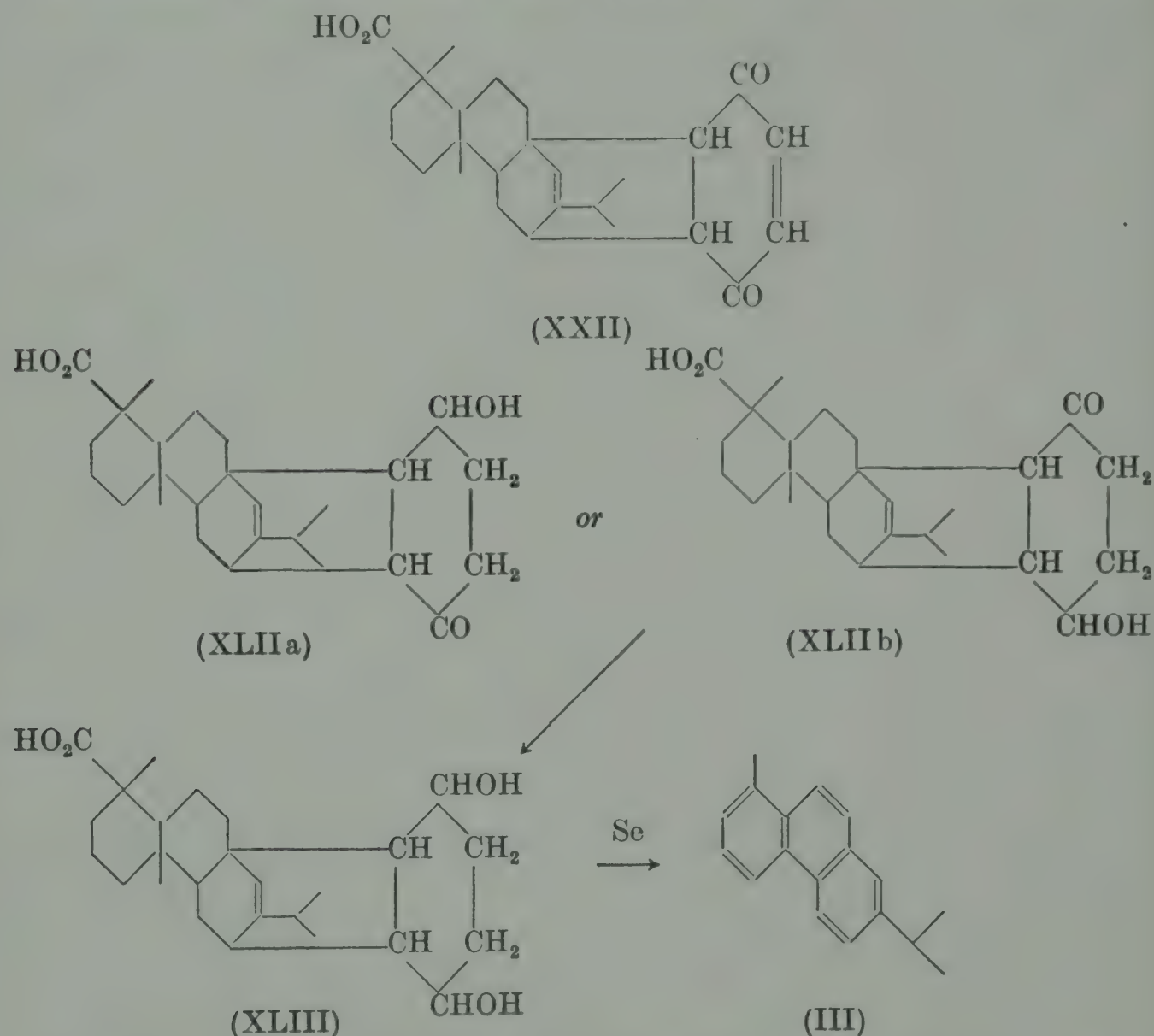
* Wienhaus and Sandermann, *Ber.* 1936, **69**, 2202.

† *Helv. Chim. Acta*, 1940, **23**, 1357.

‡ *Ibid.* 1938, **21**, 583.



Later Ruzicka and Lalande,* who confirmed the presence of a carbonyl group in the ester, $C_{25}H_{34}O_8$, by studying its ultra-violet absorption spectrum, suggested the alternative formulae (XXXVIII) or (XXXIX), when the dicarboxylic acid obtained on Clemmensen reduction would be (XL) or (XLI). Each of the latter would yield retene on dehydrogenation.



Ruzicka and Kaufmann† have studied the chemistry of the adduct (XXII), formed from levopimaric acid and *p*-benzoquinone (see p. 436). On catalytic hydrogenation in ethyl acetate solution with a platinum catalyst it afforded a *tetrahydro*-derivative, $C_{26}H_{38}O_4$, presumably (XLIIa) or (XLIIb), m.p. $260-264^\circ$, *acetate*, m.p. $209-213^\circ$, in which the presence of the ketonic grouping was detected spectroscopically, and which was reduced further by catalytic hydrogenation in acetic acid solution

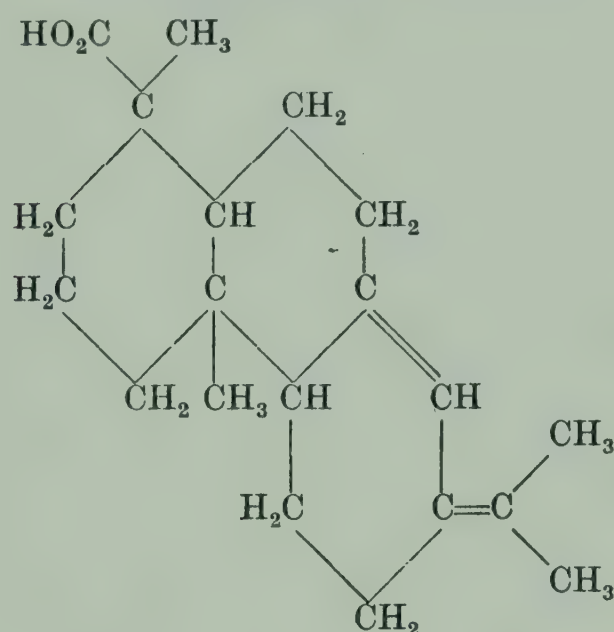
* *Loc. cit.*

† *Helv. Chim. Acta*, 1941, **24**, 1425; compare Wienhaus and Sandermann, *Ber.* 1936, **69**, 2204.

to a *hexahydro*-derivative, $C_{26}H_{40}O_4$ (XLIII), m.p. 202–205°, giving retene (III) on dehydrogenation with selenium.

The action of heat on levopimaric acid first causes isomerisation to abietic acid and then disproportionation to pyroabietic acid (see p. 416) and decarboxylation to a mixture of abietin and abietene (see p. 419) depending upon how drastic are the conditions.*

NEOABIETIC ACID



This interesting resin acid is a primary constituent of the oleo-resin (see p. 380) of *Pinus palustris* and has been isolated therefrom by Harris and Sanderson† as well as from the rosin of this tree. It is also conveniently prepared by heating abietic acid at 300° in an inert atmosphere for short periods of time. Neoabietic acid is separated from unreacted abietic acid by precipitating the latter from acetone solution as the diamylamine salt. The resin acids in the mother liquors from this operation are converted to the butanolamine salts which by crystallisation furnish the *butanolamine salt* of *neoabietic acid*, $[\alpha]_D^{24} + 102^\circ$ (in alcohol). On treatment with boric acid this gives pure *neoabietic acid* (I), $C_{20}H_{30}O_2$, m.p. 167–169°, $[\alpha]_D^{24} + 159^\circ$ (in alcohol), *methyl ester*, m.p. 61.5–62°.

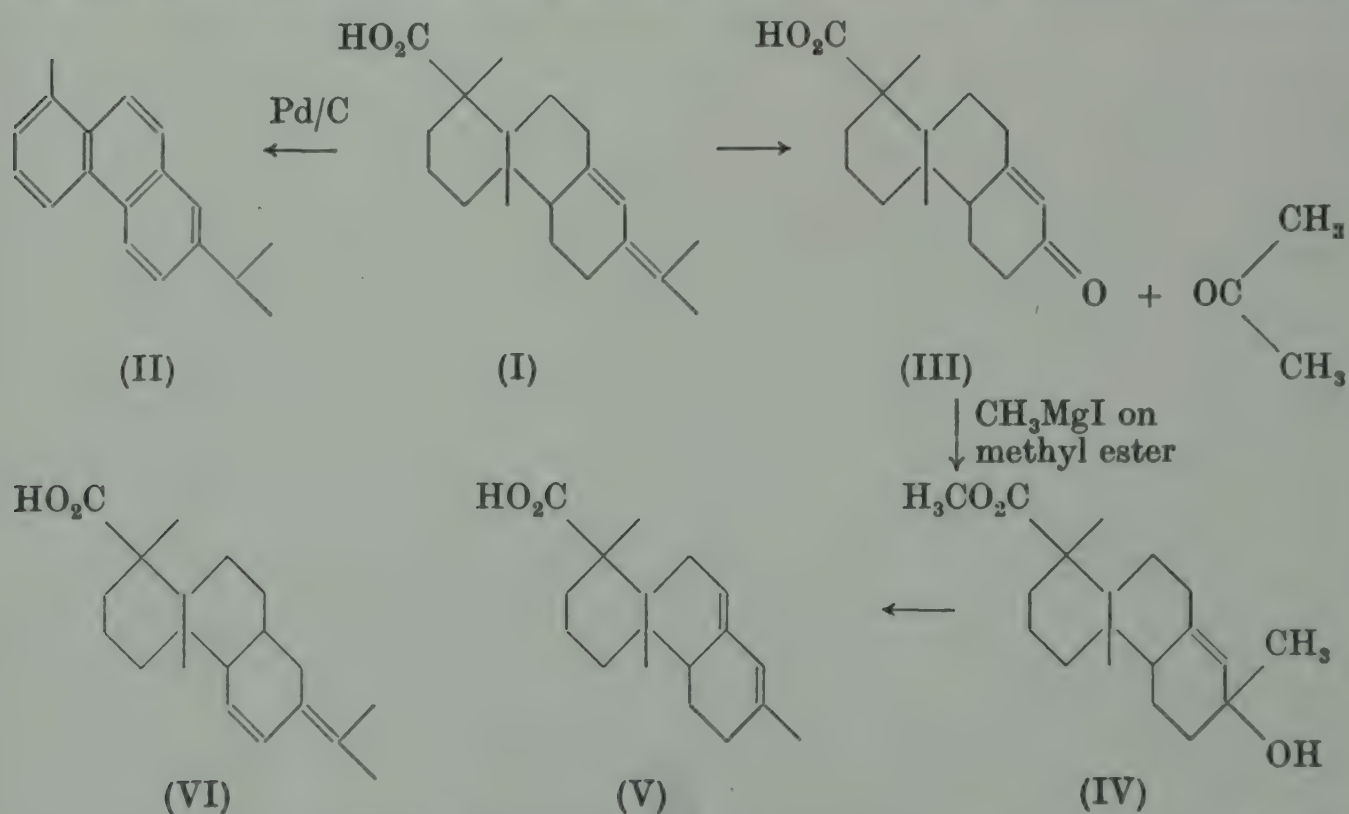
The structure of neoabietic acid has been established by Harris and Sanderson‡ in the following way. Neoabietic acid (I) gave retene (II) on dehydrogenation, absorbed two molecules of

* See Ruzicka, Balas and Vilim, *Helv. Chim. Acta*, 1924, **7**, 458.

† *J. Amer. C.S.* 1948, **70**, 334.

‡ *Ibid.*

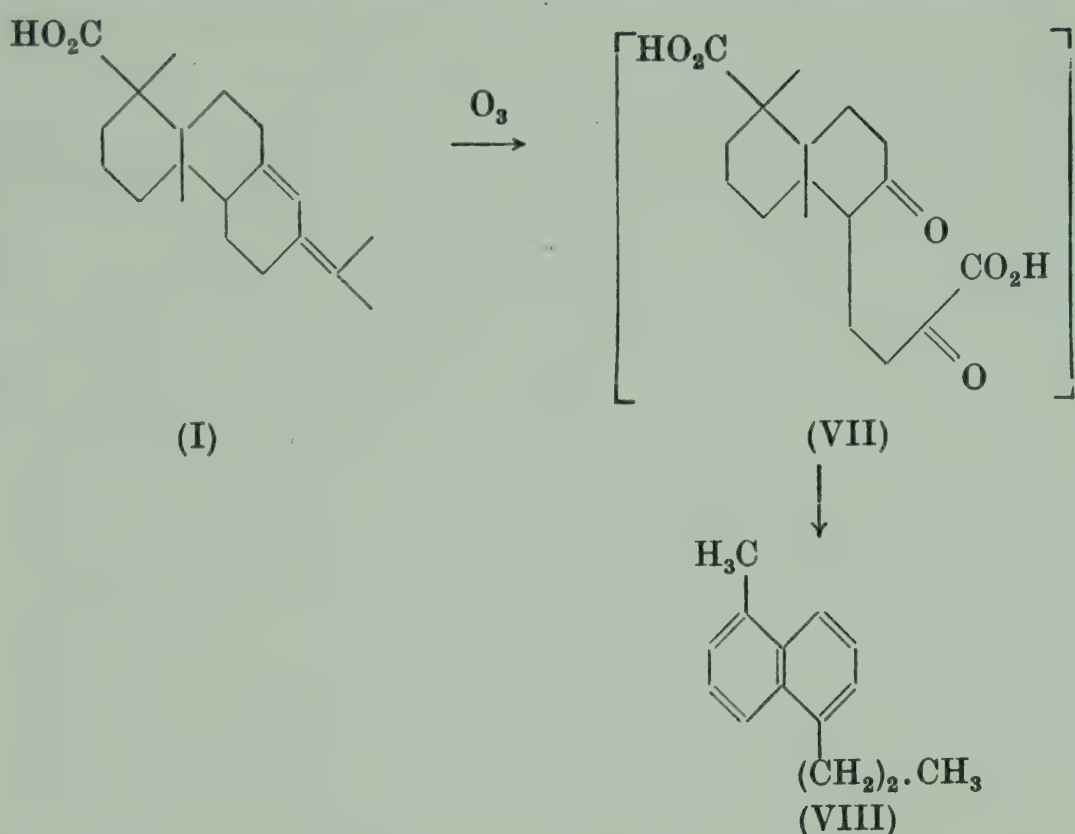
hydrogen on catalytic hydrogenation, showed an intense band in the ultra-violet at $250\text{ m}\mu$ and like levopimaric acid (see p. 429) was almost quantitatively isomerised to abietic acid by the action of mineral acid.* It must, therefore, be a simple double bond isomer of abietic acid in which the double bonds are in conjugation with each other but not in the same ring of the carbon skeleton. On ozonolysis neoabietic acid afforded acetone and an $\alpha:\beta$ -unsaturated ketone, $\text{C}_{17}\text{H}_{24}\text{O}_3$ (III), m.p. $187\text{--}188^\circ$, 2:4-dinitrophenylhydrazone, m.p. $221\text{--}222^\circ$, methyl ester (IIIa), m.p. $127\text{--}128^\circ$. By treatment with methyl magnesium iodide, the methyl ester (IIIa) was converted to a tertiary alcohol, $\text{C}_{19}\text{H}_{30}\text{O}_3$ (IV), m.p. $100\text{--}102^\circ$, which absorbed only one molecular proportion of hydrogen on catalytic hydrogenation and which gave an unsaturated acid, $\text{C}_{18}\text{H}_{26}\text{O}_2$ (V), m.p. $187\text{--}190^\circ$, $[\alpha]_D^{24} -125^\circ$ (in alcohol) by dehydration with acetyl chloride followed by alkaline hydrolysis. These experiments prove the presence of an isopropylidene group in conjugation with an olefinic linkage,



but they do not distinguish between formula (I) and formula (VI) for neoabietic acid. A distinction was possible in favour of (I) on the basis of absorption spectra because, by analogy, (I) should show an absorption maximum at $\sim 252\text{ m}\mu$ and (VI) one at $\sim 242\text{ m}\mu$. Such distinction was confirmed by drastic ozonolysis

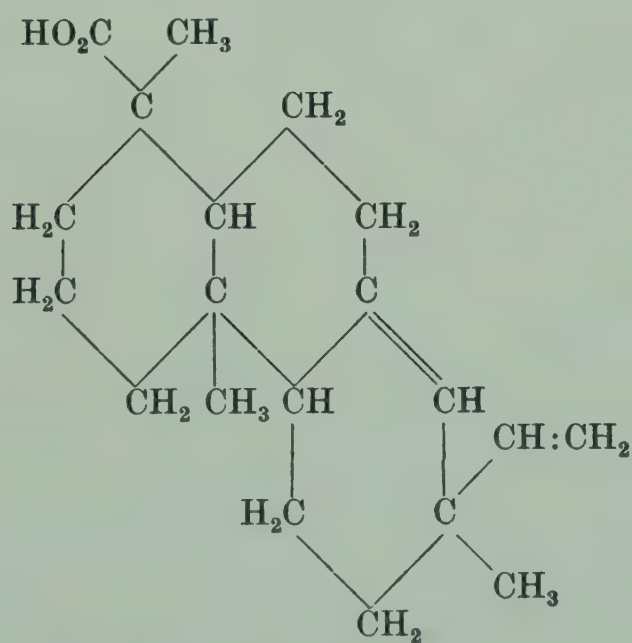
* The kinetics of this reaction have been studied by Ritchie and McBurny, *J. Amer. C.S.* 1950, 72, 1197.

of neoabietic acid, decomposition of the ozonide with water to give (VII), and dehydrogenation of the latter to give 1-methyl-5-n-propylnaphthalene (VIII), trinitrobenzoate, m.p. 82–84°.



In 1944 Lombard* isolated a resin acid from the galipot of *Pinus halepensis* for which he suggested the name *dextrosapinic acid*.† Recently Frey and Lombard‡ have shown that this acid is actually a mixture of abietic acid with neoabietic acid.

d-PIMARIC ACID



* *Compt. rend.* 1944, **219**, 587.

† Lombard, *ibid.* 1944, **219**, 253; 1946, **222**, 237; *Bull. Soc. Chim.* 1945 [v], **12**, 395; 1948 [v], **15**, 1186.

‡ *Compt. rend.* 1950, **231**, 445.

d-Pimaric acid, one of the primary resin acids (see p. 380), was first isolated by Cailliot* from French galipot, which is mainly obtained from the oleoresin exuded by the cluster pine, *Pinus maritima*; the name by which this resin acid is still known was first suggested by this author. Cailliot did not succeed in obtaining the acid in a state of purity, but this was effected at a later date by Vesterberg,† who showed the acid to have the molecular formula $C_{20}H_{30}O_2$. *d*-Pimaric acid has also been isolated from the oleoresin of *Pinus palustris*,‡ and of *P. sylvestris*§ but French galipot remains the most convenient source of this acid.|| *d*-Pimaric acid is probably present to a greater or lesser extent in all resins obtained from conifers, but it is not always possible to separate it from the accompanying isomeric resin acids (see p. 378). Thus it has been detected in the resins from *Pinus caribaea*, *P. Taeda*, *P. serotina* and *Picea excelsa*¶ as well as in the sources mentioned above. Unlike the other primary resin acids (see p. 380) *d*-pimaric acid is comparatively stable to heat and is not isomerised by treatment with mineral acids.** It is therefore more readily obtained pure than levopimaric acid (see p. 428), but nevertheless the physical constants recorded for the pure acid vary somewhat.

Although the acid is generally considered to have m.p. 211–212°, $[\alpha]_D + 60^\circ$ (in alcohol), $+ 75^\circ$ (in chloroform or benzene),†† somewhat higher values, m.p. 218–219°, $[\alpha]_D^{20} + 73.3^\circ$ (in alcohol), $+ 87.3^\circ$ (in chloroform), have also been recorded.**

* *Bull. Soc. chim.* 1874 [ii], 21, 387; compare Valente, *Atti R. Accad. Lincei*, 1884, 1, 13.

† *Ber.* 1885, 18, 3331; *ibid.* 1886, 19, 2167; compare Haller, *Ber.* 1885, 18, 2165, Vesterberg, *Ber.* 1887, 20, 3248; *idem, ibid.* 1905, 38, 4125; Dupont, *Bull. Soc. chim.* 1921 [iv], 29, 718; Knecht and Hibbert, *J. Soc. Dyers and Colourists*, 1922, 38, 221; Ruzicka and Balas, *Helv. Chim. Acta*, 1923, 6, 677; Ruzicka, Balas and Vilim, *ibid.* 1924, 7, 458.

‡ Palkin and Harris, *J. Amer. C.S.* 1933, 55, 3677; Kraft, *Annalen*, 1935, 520, 133; *idem, ibid.* 1936, 524, 1; compare Rimbach, *Ber. Pharm. Ges.* 1896, 6, 61.

§ Vesterberg, *Ber.* 1905, 38, 4125; compare Ducommon, *Chem. Zeit.* 1885, p. 1592.

|| Compare Lombard, *Bull. Soc. chim.* 1946 [v], 13, 109.

¶ See *inter al.* Hasselström and Bogert, *J. Amer. C.S.* 1935, 57, 2118; Kraft, *loc. cit.*; Sandermann, *Ber.* 1938, 71, 2005; *idem, ibid.* 1942, 75, 174.

** Compare *inter al.* Vesterberg, *Ber.* 1886, 19, 2167; *idem, ibid.* 1907, 40, 120; Rouin, *Bull. Inst. Pin*, 1929, p. 124; Krestinskii *et al.*, *J. Appl. Chem. U.S.S.R.* 1939, 12, 1840; and see p. .

†† Compare Sandermann, *Ber.* 1942, 75, 174.

** Palkin and Harris, *J. Amer. C.S.* 1933, 55, 3677; compare Balas, *Casopis Cesk. Lekarnictva*, 1927, 7, 320; Fleck and Palkin, *J. Amer. C.S.* 1940, 62, 2044; Ruzicka and Sternbach, *Helv. Chim. Acta*, 1940, 23, 124.

The first insight into the carbon skeleton present in *d*-pimaric acid was obtained by Ruzicka and Balas,* who showed that on dehydrogenation with sulphur it gave an aromatic hydrocarbon, *pimanthrene*, $C_{16}H_{14}$, m.p. 86° , *picrate*, m.p. $131-132^{\circ}$, *styphnate*, m.p. 159° , found later by Ruzicka, de Graaff and Hosking† to be 1:7-dimethylphenanthrene (I).‡

On evidence which must now be discussed *d*-pimaric acid has been represented by (II). *d*-Pimaric acid contains two ethylenic linkages as has been shown by catalytic hydrogenation and by treatment with per-acid, and it must therefore be tricyclic. On catalytic hydrogenation, suitably in ethyl acetate using a platinum catalyst, a *dihydro-d-pimaric acid*, $C_{20}H_{32}O_2$ (III), is obtained, whilst by using acetic acid as solvent a mixture of saturated *tetrahydro-d-pimaric acids* (IV), m.p.s from $220-223^{\circ}$ to $236-237^{\circ}$, results.§ Rather discordant values, between $228-229^{\circ}$ and $249-250^{\circ}$, have been recorded for the melting-point of *dihydro-d-pimaric acid*, but m.p. $240-241^{\circ}$, $[\alpha]_D$ ca. $+17^{\circ}$ (in alcohol), *methyl ester*, m.p. $79-80^{\circ}$, $[\alpha]_D +19^{\circ}$ (in benzene) is usually accepted as representing the pure acid.|| It has been suggested that *dihydro-d-pimaric acid* is a mixture of stereoisomers, but this is difficult to reconcile with the formula (III), and it is probable that the *d*-pimaric acid used in the experiment was not completely homogeneous.¶

By the action of perbenzoic acid on methyl *d*-pimarate (see p. 455) a *monoxide*, $C_{20}H_{30}O_3$ (V), b.p. 180° (bath temperature)/0.08 mm., has been prepared, one of the ethylenic linkages not being attacked.** Treatment of methyl *dihydro-d-pimarate* with perbenzoic acid at low temperatures under somewhat different conditions gave two *monoxides*, $C_{20}H_{32}O_3$ (VI), m.p.s $103-104^{\circ}$ and $118-119^{\circ}$ respectively. By the action of sulphuric acid in

* *Helv. Chim. Acta*, 1923, **6**, 677; compare *idem, ibid.* 1924, **7**, 875.

† *Ibid.* 1931, **14**, 233.

‡ For the synthesis of this hydrocarbon see Haworth, Letsky and Mavin (*J.C.S.* 1932, p. 2520), and Bardhan and Sengupta (*ibid.* p. 2520; compare Ruzicka and Waldmann, *Helv. Chim. Acta*, 1932, **15**, 907).

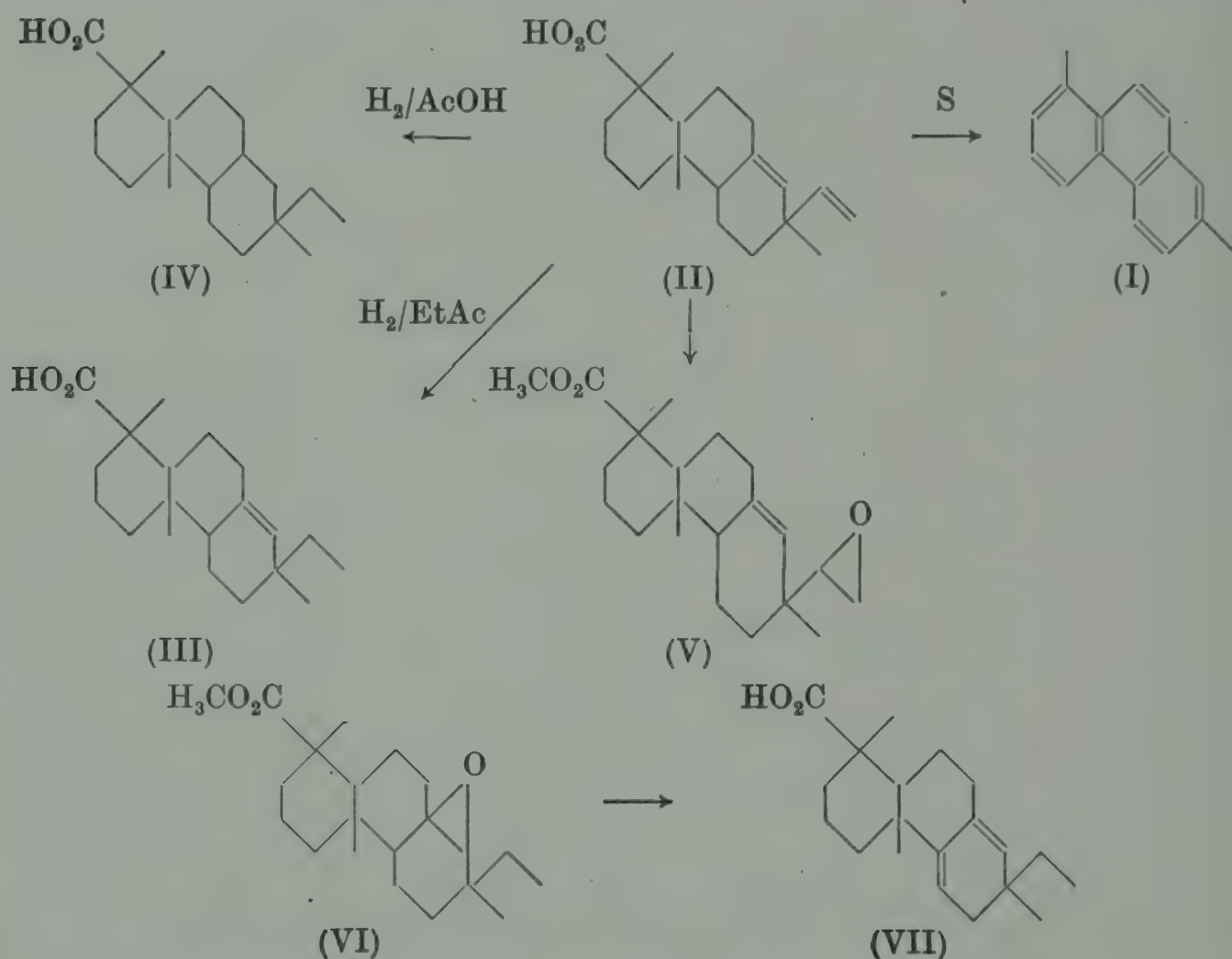
§ Ruzicka, Huyser and Seidel, *Rec. trav. Chim.* 1928, **47**, 363.

|| Ruzicka and Balas, *Helv. Chim. Acta*, 1923, **6**, 681; Ruzicka, Huyser and Seidel, *loc. cit.*; Ruzicka and Frank, *Helv. Chim. Acta*, 1932, **15**, 1294; Palkin and Harris, *J. Amer. C.S.* 1933, **55**, 3677; Hasselström and Bogert, *ibid.* 1935, **57**, 2118; compare Tschugaeff and Teearu, *Ber.* 1913, **46**, 1773.

¶ See Ruzicka, Huyser and Seidel, *loc. cit.*

** Ruzicka, Huyser and Seidel, *loc. cit.*; Ruzicka and Frank, *loc. cit.*; Ruzicka and Sternbach, *Helv. Chim. Acta*, 1940, **23**, 124; Kraft, *Annalen*, 1936, **524**, 1.

acetic acid solution these monoxides are said to yield an isomer of *d*-pimaric acid, m.p. 186–188°, which is possibly represented by (VII). If methyl dihydro-*d*-pimarate is allowed to react with perbenzoic acid at room temperature the reaction proceeds in a more complicated manner to form a mixture of monoxides, dioxides and a second *isomer* of *d*-pimaric acid, m.p. 215–216°, $[\alpha]_D$ ca. +60° (in alcohol), *methyl ester*, m.p. 54–55°, $[\alpha]_D$ +52° (in benzene).* It would appear not improbable that this acid is actually a somewhat impure form of *d*-pimaric acid. Whilst these

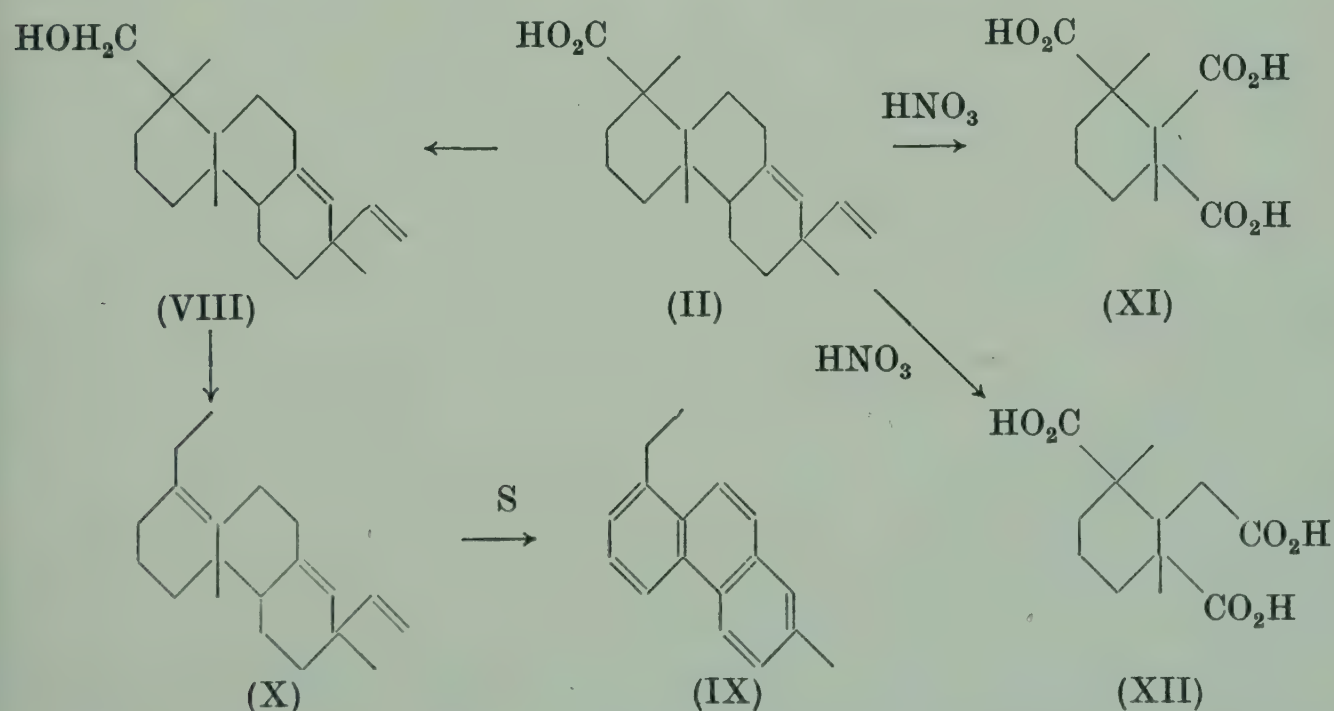


experiments prove beyond doubt that *d*-pimaric acid contains two ethylenic linkages which differ in their reactivity, they leave undetermined the position of these linkages in the molecule. Before considering the evidence bearing on this it will be convenient to give proof of the position of the carboxyl group in the molecule.

Ethyl *d*-pimarate (see below) gave on reduction by the Bouveault-Blanc method a primary alcohol, *d*-pimarinol (VIII), $C_{20}H_{32}O$, b.p. 166–168°/0.1 mm., d_4^{15} 1.0114, n_D^{15} 1.5357, which

* Ruzicka and Frank, *loc. cit.*

was dehydrated by phosphorus pentachloride to the hydrocarbon, *methyl-d-pimar*in, $C_{20}H_{30}$, b.p. $140-145^{\circ}/0.3$ mm., $d_4^{22^{\circ}}$ 0.9587, $n_D^{22^{\circ}}$ 1.5301. This was found by Ruzicka and Balas* to be dehydrogenated by sulphur to an aromatic *hydrocarbon*, $C_{17}H_{16}$, m.p. 81° , *picrate*, m.p. 115° . It was subsequently shown by Ruzicka, de Graaff and Müller† that this aromatic hydrocarbon must be 1-ethyl-7-methylphenanthrene (IX), and the correctness of this view has been proved by synthesis.‡ From this it follows that methyl-*d*-pimar*in* must be represented by (X), its formation involving a rearrangement similar to that observed in the dehydration of abietinol (see p. 386). The position of the carboxyl group in *d*-pimaric acid indicated by this experiment has been confirmed by the study of the oxidation of the resin acid with nitric acid. Two crystalline tribasic acids, $C_{11}H_{16}O_6$ (XI), m.p. $218-219^{\circ}$ and $C_{12}H_{18}O_6$ (XII), m.p. 211° , were isolated identical with those obtained from abietic acid (see p. 387) in exactly the same way.§ The fusion of rings *A* and *C* in *d*-pimaric acid must, therefore, be *trans* as has been proved for abietic acid (see p. 406).



When *d*-pimaric acid is oxidised with potassium permanganate in a glycol, *dihydroxy-d-pimaric acid*, $C_{20}H_{32}O_4$ (XIII) (see note on nomenclature, p. 391), m.p. 224° decomp., $[\alpha]_D + 6.8^{\circ}$ (in alcohol), *diacetate*, m.p. 235° , is produced, together with a small

* *Helv. Chim. Acta*, 1924, **7**, 875.

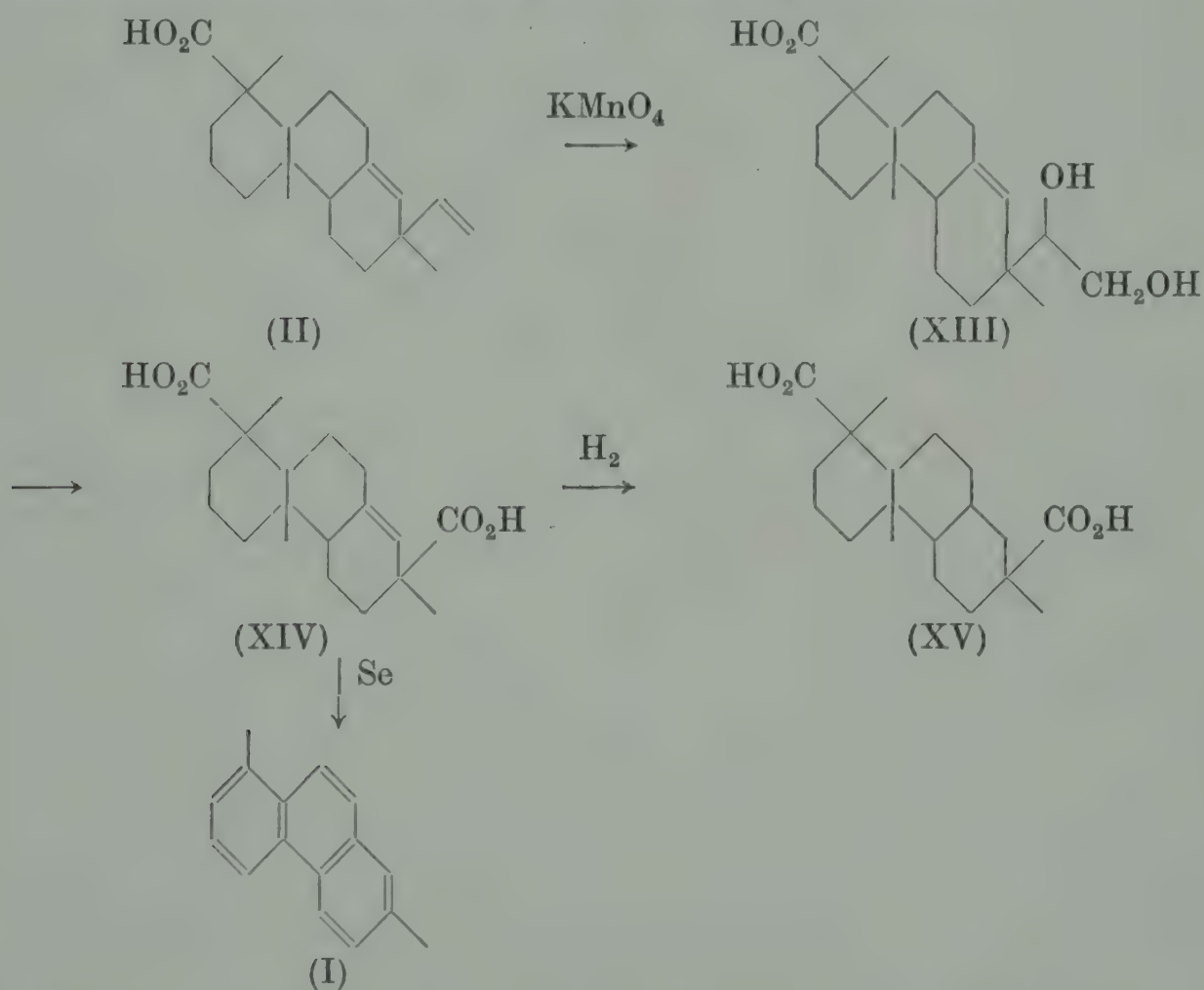
† *Ibid.* 1932, **15**, 1300.

‡ Haworth, *J.C.S.* 1932, p. 2717.

§ Ruzicka, de Graaff, Goldberg and Frank, *Helv. Chim. Acta*, 1932, **15**, 915.

amount of an isomeric *dihydroxy-acid*, m.p. 239° .^{*} On further oxidation with chromic acid the dihydroxy-acid (XIII) afforded a *dicarboxylic acid*, $C_{19}H_{28}O_4$ (XIV), m.p. $260-261^{\circ}$, which was catalytically hydrogenated to the saturated *dihydrodicarboxylic acid*, $C_{19}H_{30}O_4$ (XV), m.p. $210-220^{\circ}$, and which furnished pimanthrene (I) on dehydrogenation by heating with selenium.[†]

The formation of the dicarboxylic acid (XIV), from the glycol (XIII), and the dehydrogenation of *d*-pimaric acid to pimanthrene can only be explained if *d*-pimaric acid contains a vinyl grouping attached to a tertiary carbon atom. Confirmation of the presence of a vinyl group has been obtained by ozonolysis when formaldehyde was produced in good yield.[‡]



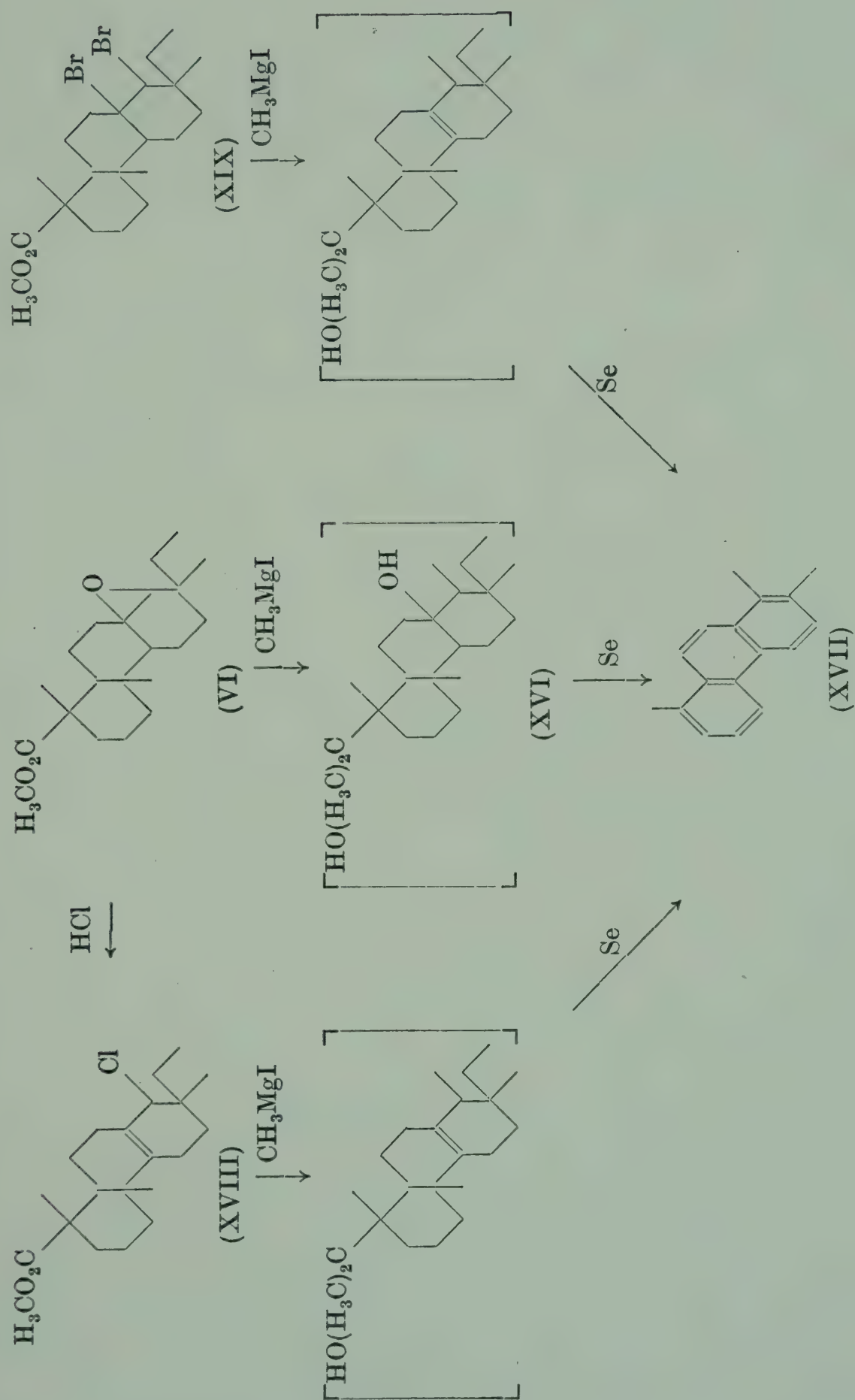
Ruzicka and Sternbach[§] have given an elegant proof of the position of the less reactive of the two ethylenic linkages in *d*-pimaric acid. By treatment of the oxide of methyl dihydro-*d*-pimarate (VI) with methyl magnesium iodide an *alcohol* (XVI)

^{*} Ruzicka and Balas, *Annalen*, 1928, **460**, 202; compare Levy, *Ber.* 1928, **61**, 616.

[†] Ruzicka, de Graaff, Goldberg and Frank, *loc. cit.*

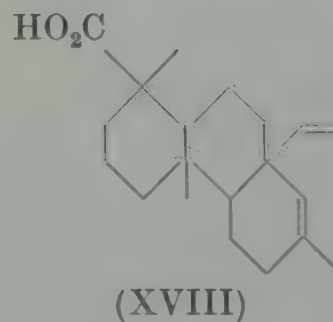
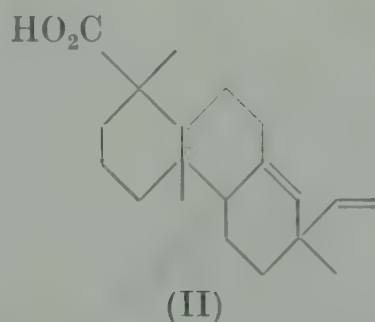
[‡] Ruzicka and Balas, *Annalen*, 1928, **460**, 202; compare Komshilov, *Lesokhim. Prom.* 1940, **3**, No. 6, p. 25.

[§] *Helv. Chim. Acta*, 1940, **23**, 124.



was prepared which on dehydrogenation with selenium gave 1:7:8-trimethylphenanthrene (XVII). Methyl dihydro-*d*-pimarate was also converted into this hydrocarbon by two other routes. By the action of hydrogen chloride on the oxide-ester (VI), methyl-8-chloroisodihydro-*d*-pimarate, $C_{21}H_{33}O_2Cl$ (XVIII), m.p. 122–125°, was prepared, yielding on treatment with methyl magnesium iodide a substance which gave 1:7:8-trimethylphenanthrene (XVII) on dehydrogenation with selenium. By a similar series of reactions methyl dihydro-*d*-pimarate dibromide (XIX) was likewise converted into the trimethyl hydrocarbon.

It is clear from all these experiments, taken in conjunction with the isoprene rule, that *d*-pimaric acid must be represented by either (II) or (XVIII). Ruzicka and Sternbach* preferred (XVIII) since, according to Frank,[†] tetrahydro-*d*-pimaric acid on dehydrogenation gave exclusively pimanthrene and no 1-methyl-7-ethylphenanthrene. On the other hand Fleck and Palkin[‡] regarded (II) as the more probable formula, since they were able to show that *d*-pimaric acid, on treatment with concentrated sulphuric acid, yielded a saturated *hydroxy-lactone*, $C_{20}H_{32}O_3$, m.p. 181–182°, $[\alpha]_D^{20} - 4^\circ$ (in alcohol), from which they prepared the corresponding *dihydroxy-acid*, $C_{20}H_{34}O_4$, m.p. 150–151°, *methyl ester*, m.p. 156–157°. Support for Fleck and Palkin's view was provided by the observation of Hasselström and Hampton[§] that dihydro-*d*-pimaric acid also formed a *lactone*, $C_{20}H_{23}O_2$, m.p. 143–144°, $[\alpha]_D - 40^\circ$ (in alcohol), by treatment with cold concentrated sulphuric acid. These lactones are more readily formulated on the basis of (II) even though their formation very probably involves a molecular rearrangement (see p. 410).



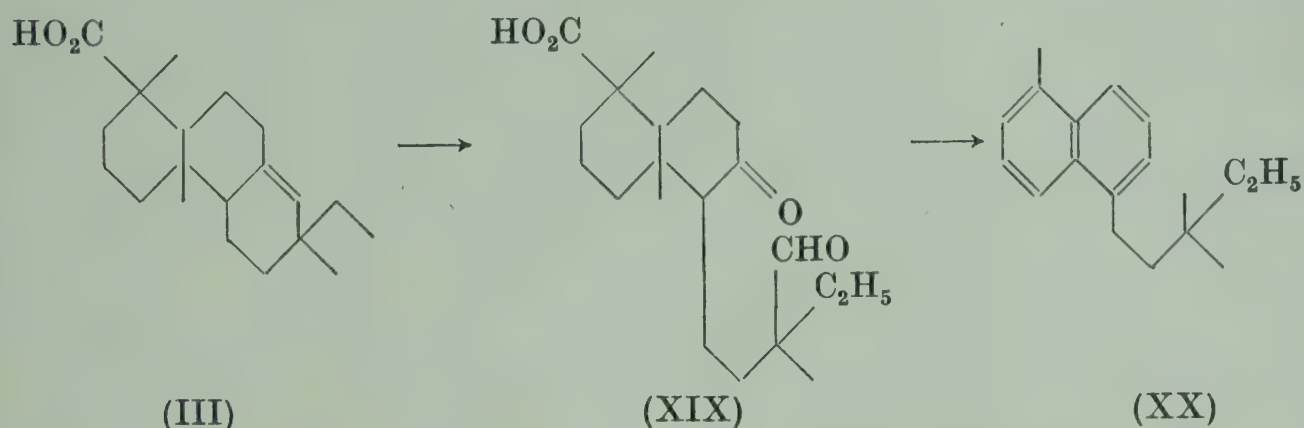
* *Loc. cit.*

[†] Dissertation, E. T. H. Zurich, 1933, p. 27; compare Ruzicka, de Graaff and Müller, *Helv. Chim. Acta*, 1932, **15**, 1300.

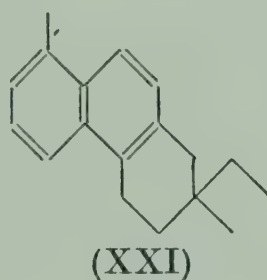
[‡] *J. Amer. C.S.* 1940, **62**, 2044.

[§] *Ibid.* 1939, **61**, 967.

Conclusive evidence in favour of formula (II) has recently been obtained by Harris and Sanderson.* Dihydro-*d*-pimaric acid (III) was ozonised, and the product (XIX) reduced by the Wolff-Kishner method and then dehydrogenated to give a naphthalenic hydrocarbon (XX), $C_{18}H_{24}$, trinitrobenzene *adduct*, m.p. 113–116°. The alternative formula (XVIII), for *d*-pimaric acid, would have led to a C_{16} naphthalenic hydrocarbon in the



above degradation. Further evidence for the correctness of (II) was provided by the observation that partial dehydrogenation of *d*-pimaric acid using palladised charcoal gave a trisubstituted naphthalenic hydrocarbon (XXI), $C_{18}H_{22}$, trinitrobenzene *adduct*, m.p. 122–123°, further dehydrogenated to give pimanthrene.



d-Pimaric acid can be characterised by its physical constants (see above) and by the preparation of the *methyl ester*, m.p. 69°, b.p. 149–150°/0.03 mm., d_4^{19} 1.030, n_D^{19} 1.5208, the *ethyl ester*, m.p. 52°, b.p. 169–170°/0.2 mm., d_4^{14} 1.013, n_D^{14} 1.5151, and the *nitrosite*, m.p. 79–80°.† The acid is most easily detected in mixtures of resin acids by catalytic hydrogenation to the dihydro-acid (VI), which is readily isolated, since it is sparingly soluble in methanol.‡

* *J. Amer. C.S.* 1948, **70**, 2081.

† Vesterberg, *Ber.* 1886, **19**, 2171; Ruzicka and Balas, *Helv. Chim. Acta*, 1923, **6**, 677; *idem*, *Annalen*, 1928, **460**, 202.

‡ Compare Hasselström and Bogert, *loc. cit.*; Levy, *Ber.* 1928, **61**, 616

Balas* has described the formation of a number of highly crystalline salts from *d*-pimaric acid and various primary and secondary amines. These may also prove useful for the characterisation of the acid. A polarimetric method for the quantitative determination of *d*-pimaric acid in resin acid mixtures has been described by Sandermann† and the feasibility of its quantitative determination by ozonolysis and the estimation of the formaldehyde and formic acid produced, has been suggested by Komshilov.‡ The X-ray crystallography of *d*-pimaric acid has been studied by Sevast'yanov and Zhdanov,§ whilst Harkins, Ries and Carmen|| have examined the surface films formed by *d*-pimaric acid and tetrahydro-*d*-pimaric acid.

By the action of hydrogen chloride on *d*-pimaric acid three *monohydrochlorides*, m.p. 232° decomp., $[\alpha]_D + 13.6^\circ$ (in alcohol), m.p. 184° decomp., $[\alpha]_D + 47.3^\circ$ (in alcohol), and m.p. 125°, $[\alpha]_D - 20.5^\circ$ (in alcohol), are said to be formed,¶ and the parent acid has been regenerated from the second of these by heating with quinoline. As would be expected from the formula (II) *d*-pimaric acid does not form a normal adduct with maleic anhydride, but only an ill-defined, polymeric condensation product.** By the prolonged heating of *d*-pimaric acid, or, more conveniently, the acid chloride, a triply unsaturated hydrocarbon, *d*-pimarín, $C_{19}H_{28}$, b.p. 182–184°/12 mm., $d_4^{15^\circ} 0.9693$, $n_D^{15^\circ} 1.5349$, $\alpha_D + 109^\circ$, is obtained. This substance is the analogue of abietin (see p. 419).†† *d*-Pimarín is stated by Ruzicka and Balas to be dehydrogenated by heating with alcoholic sulphuric acid, to a benzenoid *hydrocarbon*, $C_{19}H_{26}$, b.p. 203–212°/12 mm., $d_4^{15^\circ} 0.9863$, $n_D^{15^\circ} 1.5505$, but this view may require revision in the light of the more recent work in this field.

* *Casopis Cesk. Lekarnictva*, 1927, **7**, 320.

† *Seifensieder Ztg.*, 1937, **64**, 402, 421; *Ber.* 1938, **71**, 2005; *ibid.* 1942, **75**, 174.

‡ *Loc. cit.*

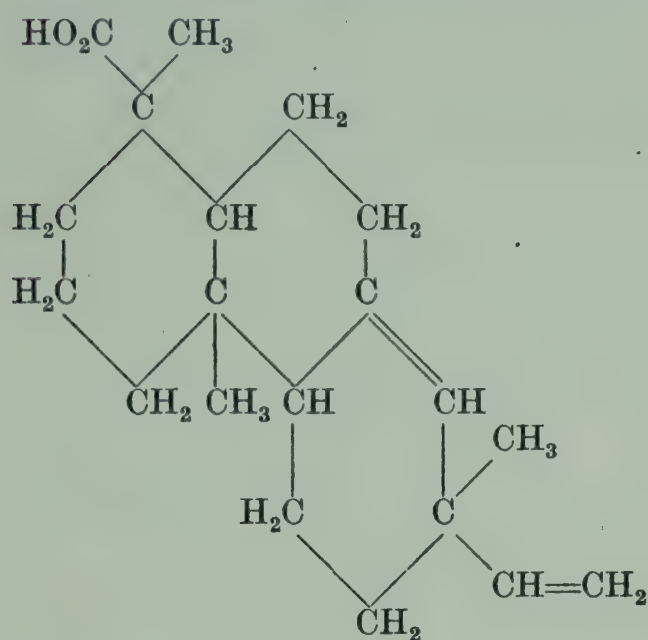
§ *Acta Physicochimica, U.S.S.R.* 1942, **16**, 59.

|| *J. Amer. C.S.* 1935, **57**, 2224; compare Harkins, *Pub. Am. Assoc. Adv. Sci.* 1939, No. 7, p. 19.

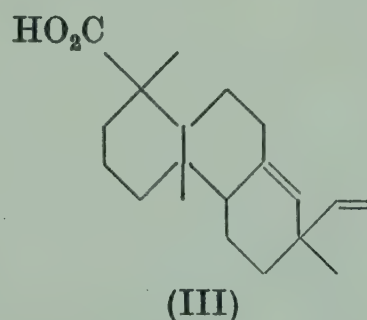
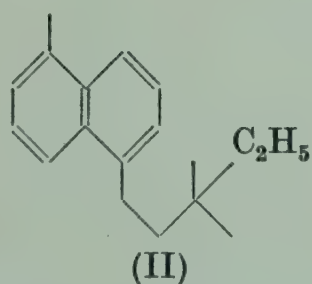
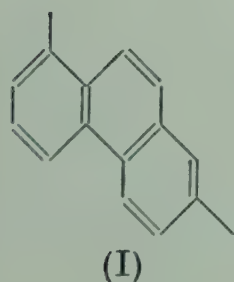
¶ Ruzicka and Balas, *Annalen*, 1928, **460**, 202; Balas, *Casopis Cesk. Lekarnictva*, 1927, **7**, 320.

** Ruzicka, Ankersmit and Frank, *Helv. Chim. Acta*, 1932, **15**, 1289.

†† Ruzicka and Balas, *ibid.* 1924, **7**, 875; compare Vesterberg, *Ber.* 1886, **19**, 2167; 1907, **40**, 120; Ruzicka and Schinz, *Helv. Chim. Acta*, 1923, **6**, 662, 833.

ISO-*d*-PIMARIC ACID

iso-*d*-Pimaric acid, $C_{20}H_{30}O_2$, m.p. 162–164°, $[\alpha]_D^{24} \pm 0^\circ$, methyl ester, m.p. 61.5–62°, was isolated by Harris and Sanderson* as the butanolamine salt, $[\alpha]_D^{24} \pm 0^\circ$, from the oleoresin of *Pinus palustris* and from wood and gum rosin. In many respects the behaviour of iso-*d*-pimaric acid paralleled very closely that of *d*-pimaric acid. Thus it gave formaldehyde on ozonolysis, pimanthrene (I) on dehydrogenation and a dihydro-acid, $C_{20}H_{32}O_2$, m.p. 173–175°, $[\alpha]_D^{24} \pm 0^\circ$, on partial catalytic hydrogenation. Furthermore, degradation of dihydro-iso-*d*-pimaric acid in the same way as is described on p. 455 for dihydro-*d*-pimaric acid led to the same naphthalenic hydrocarbon (II). Harris and Sanderson† suggested that iso-*d*-pimaric acid is epimeric to *d*-pimaric acid (III) at C₇ and thus has the formula (IV) (p. 458). In

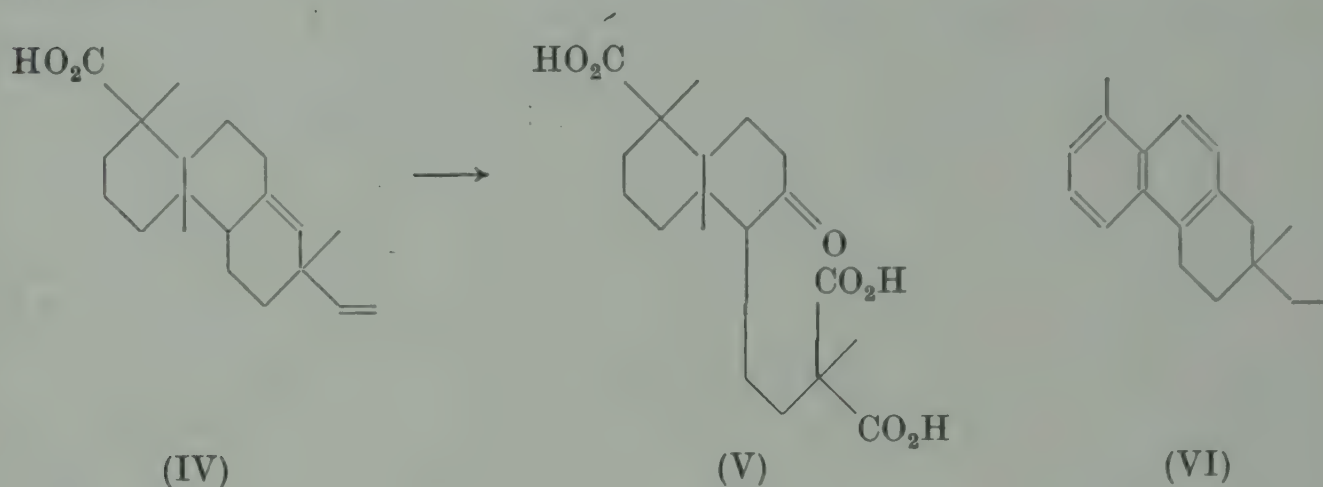


support of this formula they showed that ozonolysis of both *d*- and iso-*d*-pimaric acids afforded the same keto-tricarboxylic acid (V), $C_{19}H_{28}O_7$, dinitrophenylhydrazone, m.p. 185–188°, semicarbazone, m.p. 223–225°. In the formation of this substance the

* *J. Amer. C.S.* 1948, **70**, 2079.

† *Ibid.* 1948, **70**, 2081.

asymmetry at C₇ is destroyed. Furthermore partial dehydrogenation of *iso-d*-pimaric acid furnished the same trisubstituted naphthalenic hydrocarbon (VI) as was obtained (p. 455) in the same way from *d*-pimaric acid. In both methods of preparation racemisation must occur since the products were optically inactive.



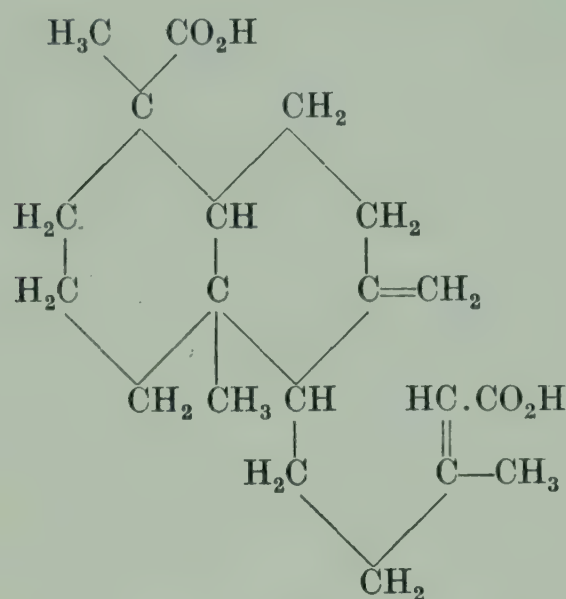
Recently Harris and Sanderson* have described the isolation of an *aldehyde*, C₂₀H₃₀O, m.p. 50–52°, *semicarbazone*, m.p. 223–225°, *2:4-dinitrophenylhydrazone*, m.p. 192–194°, from the neutral fraction of commercial wood and gum rosins. On chromic acid oxidation this aldehyde gave *iso-d*-pimaric acid and it was designated, therefore, as *iso-d*-pimarinal. This substance is apparently identical with *cryptopinone*, C₂₀H₃₀O, m.p. 50–52°, b.p. 160–165°/0.1 mm. (bath temperature), *semicarbazone*, m.p. 223–224°, isolated earlier by Sørensen and Bruun† from the twig roots and resinified trunks of *Pinus sylvestris*.

* *J. Amer. C.S.* 1948, **70**, 3870.

† *Acta Chem. Scand.* 1947, **1**, 112.

B. DICARBOXYLIC ACID

AGATHENEDICARBOXYLIC ACID



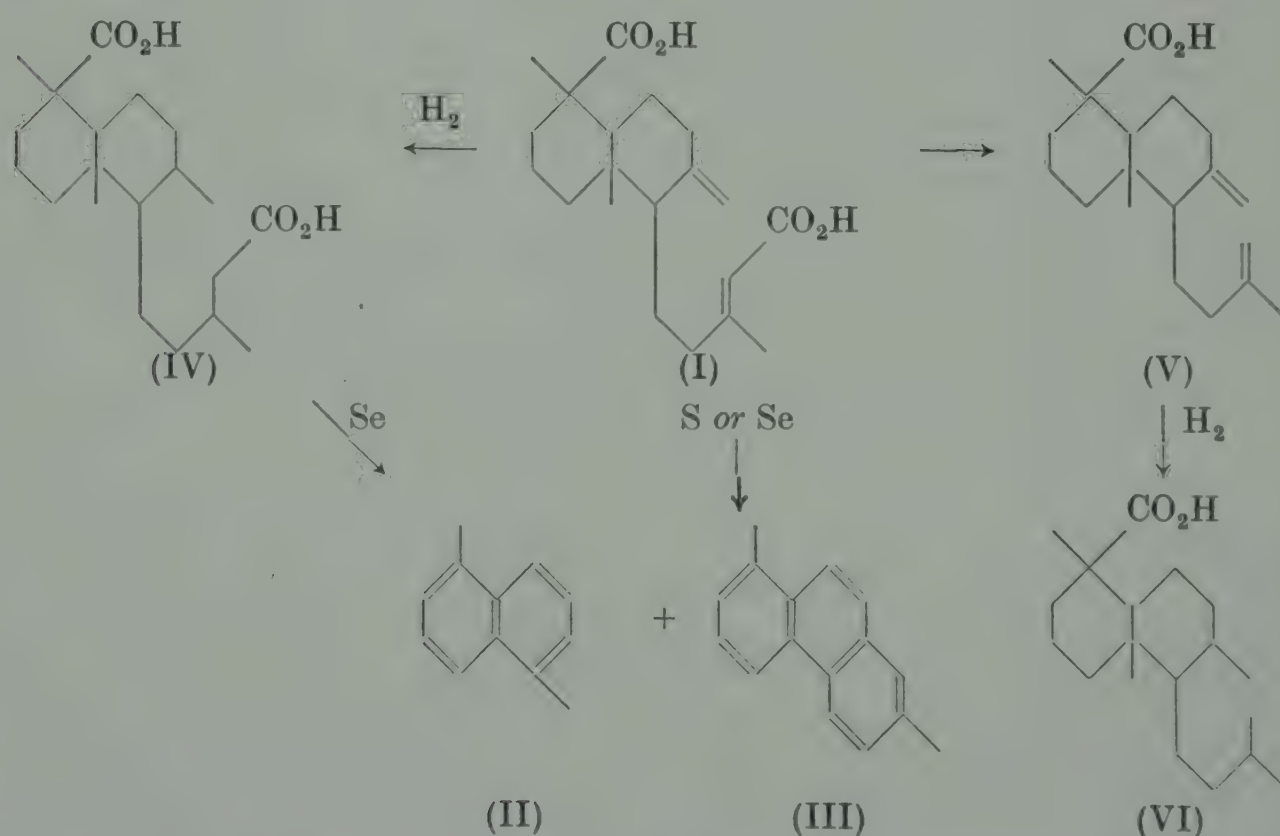
The bicyclic resin acid, *agathenedicarboxylic acid*,* $C_{20}H_{30}O_4$ (I), m.p. $203-204^\circ$, $[\alpha]_D + 52.3$ to $+ 56.1^\circ$ (in alcohol), *dimethyl ester* (Ia), b.p. $196-198^\circ/0.6$ mm., $d_4^{17^\circ} 1.077$, $n_D^{17^\circ} 1.5163$, $[\alpha]_D + 54.6$ to $+ 61.2^\circ$ (in alcohol), was first isolated in a state of purity by Ruzicka and Hosking[†] from Kauri copal and from the soft and hard grades of Manila copal.

The structure (I) which has been assigned to agathenedicarboxylic acid is based upon the following evidence. The carbon skeleton present in the acid is indicated by its dehydrogenation with sulphur to give 1:5:6-*trimethylnaphthalene* (II) and *pimanthrene* (III). The formation of the tricyclic hydrocarbon results

* It is both illogical and erroneous to name the hypothetical hydrocarbon, $C_{20}H_{34}$, *agathene* (Ruzicka and Hosking, *Annalen*, 1929, **469**, 147) and its derived diacid, agathenedicarboxylic acid. If agathene is to denote the hydrocarbon, $C_{20}H_{34}$, then the derived diacid should be called dicarboxyagathene. If, however, we regard agathene as $C_{18}H_{30}$ then the derived diacid is correctly named, but there follows a serious objection to the term noragathenemonocarboxylic acid for the acid obtained from agathenedicarboxylic acid by loss of carbon dioxide and which, on this basis, should be called simply agathenecarboxylic acid. Probably the best nomenclature would be based on the hypothetical bicyclic hydrocarbon, *agathane*, $C_{18}H_{34}$. In this case agathenedicarboxylic acid becomes agathadienedicarboxylic acid and tetrahydroagathenedicarboxylic acid becomes agathanedicarboxylic acid. In spite of these considerations, through force of custom, we have used throughout this article the nomenclature employed by Ruzicka.

[†] *Annalen*, 1929, **469**, 147; compare Tschirch and Niederstadt, *Arch. Pharm.* 1901, **239**, 145, 161; Tschirch and Koch, *ibid.* 1902, **240**, 202; Richmond, *Philippine J. Sci.* **5 A**, p. 171; Ruzicka, Steiger and Schinz, *Helv. Chim. Acta*, 1926, **9**, 962; Horrmann and Kroll, *Arch. Pharm.* 1927, **265**, 214; Scheiber, *Annalen*, 1927, **453**, 52.

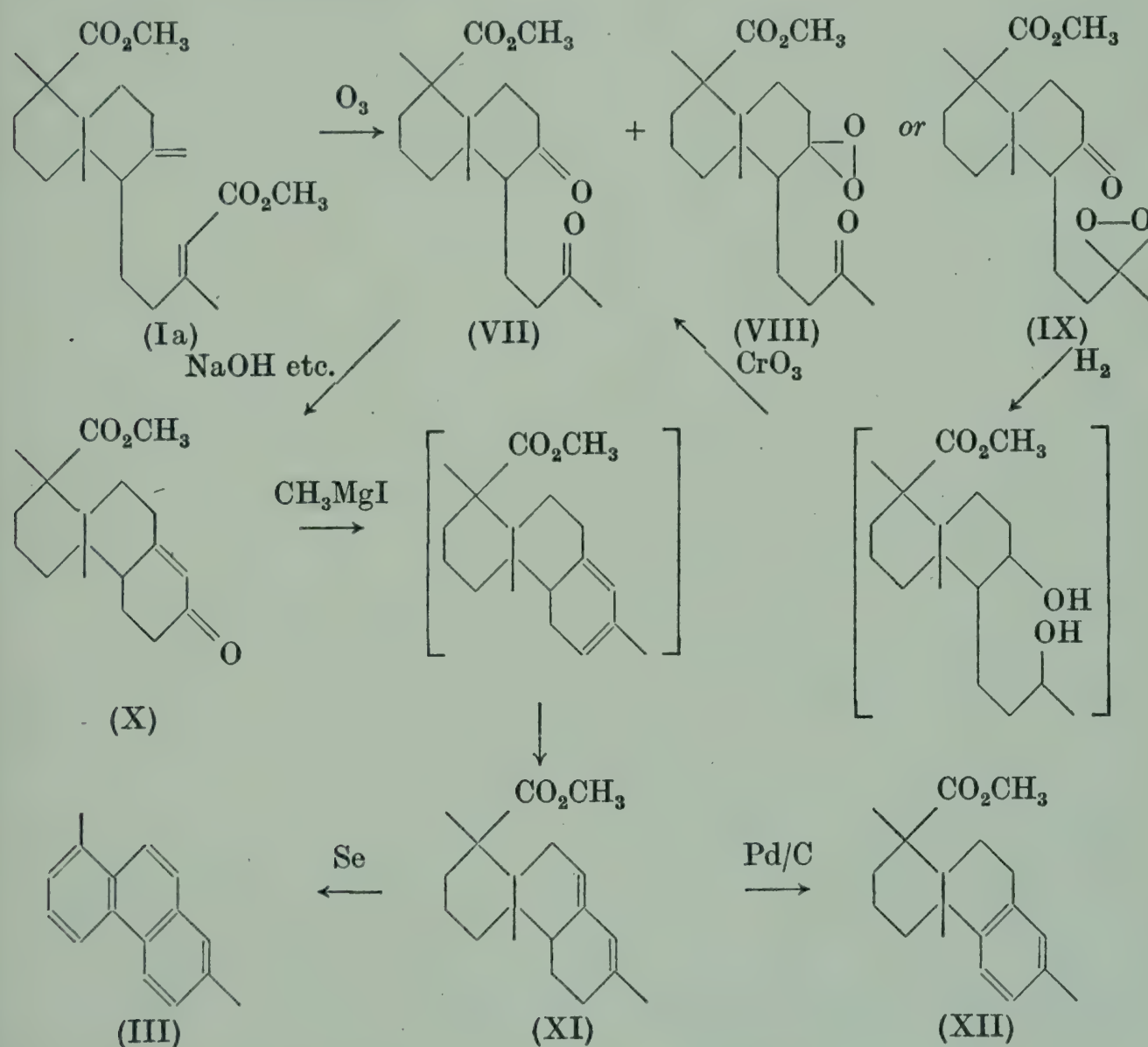
presumably from the presence of an unsaturated side chain which appears partially in the naphthalene hydrocarbon as a methyl group. On dehydrogenation with selenium, in addition to the hydrocarbons referred to above, two unidentified hydrocarbons are formed, one of these being obtained in an impure state yielding an unstable *picrate*, m.p. 210° , whilst the second was found to have the composition $C_{17}H_{20}$, m.p. 42° , b.p. $138-139^{\circ}/0.8$ mm., $d_4^{16^{\circ}}$ 1.027, $n_D^{16^{\circ}}$ 1.6056, *picrate*, m.p. 138° , *stypenate*, m.p. $153-154^{\circ}$.^{*} The acid contains two ethylenic linkages, since it yields on catalytic hydrogenation *tetrahydroagathenedicarboxylic acid*, $C_{20}H_{34}O_4$ (IV), *dimethyl ester*, b.p. $165-166^{\circ}/0.1$ mm., $d_4^{20^{\circ}}$ 1.042, $n_D^{20^{\circ}}$ 1.4914, $[\alpha]_D +42.2^{\circ}$ to $+47.9^{\circ}$ (in alcohol). This saturated acid gives on selenium dehydrogenation 1:5:6-trimethylnaphthalene and the two hydrocarbons of unknown structure referred to above but no pimanthrene. This would be anticipated if the assumption made above is correct, namely that the cyclisation is due to an ethylenic linkage in the side chain.



One of the ethylenic linkages in agathenedicarboxylic acid is in the $\alpha:\beta$ -position to one of the carboxyl groups as shown by the absorption spectrum (λ max. $220\text{ m}\mu$; $\log \epsilon = 4.2$ in alcohol) and

^{*} Ruzicka, Steiger and Schinz, *Helv. Chim. Acta*, 1926, **9**, 962; Ruzicka and Hosking, *ibid.* 1930, **13**, 1402; compare Ruzicka and Rey, *ibid.* 1943, **26**, 2136.

by the ease with which it loses carbon dioxide when it is heated above its melting-point to give *noragathenemonocarboxylic acid*, $C_{19}H_{30}O_2$ (V), m.p. 146–147°, b.p. 180–183°/0.4 mm., $[\alpha]_D + 51.3^\circ$ to $+ 59.3^\circ$ (in alcohol), *methyl ester* (Va), b.p. 151–152°/0.6 mm., $d_4^{23^\circ} 1.002$, $n_D^{23^\circ} 1.5085$, $[\alpha]_D + 57.0^\circ$ (in alcohol), yielding on catalytic hydrogenation *tetrahydronoragathenemonocarboxylic acid*, $C_{19}H_{34}O_2$ (VI), m.p. 133°, $[\alpha]_D + 50.3^\circ$ (in alcohol), *methyl ester*, m.p. 52–53°, b.p. 141–143°/0.3 mm., $d_4^{22^\circ} 0.9411$, $n_D^{22^\circ} 1.4693$, $[\alpha]_D + 53.7^\circ$ (in alcohol).*



The elegant experiments of Ruzicka, Bernold and Tallichet on the ozonolysis of dimethyl agathenedicarboxylate have shown conclusively that the two ethylenic linkages in the ester must be in the positions as shown in (Ia). Ozonolysis of the ester in acetic acid solution yielded, as the main neutral products, a *diketo-ester*,

* Ruzicka and Hosking, *Annalen*, 1929, **469**, 147; Ruzicka, Bernold and Tallichet, *Helv. Chim. Acta*, 1941, **24**, 223.

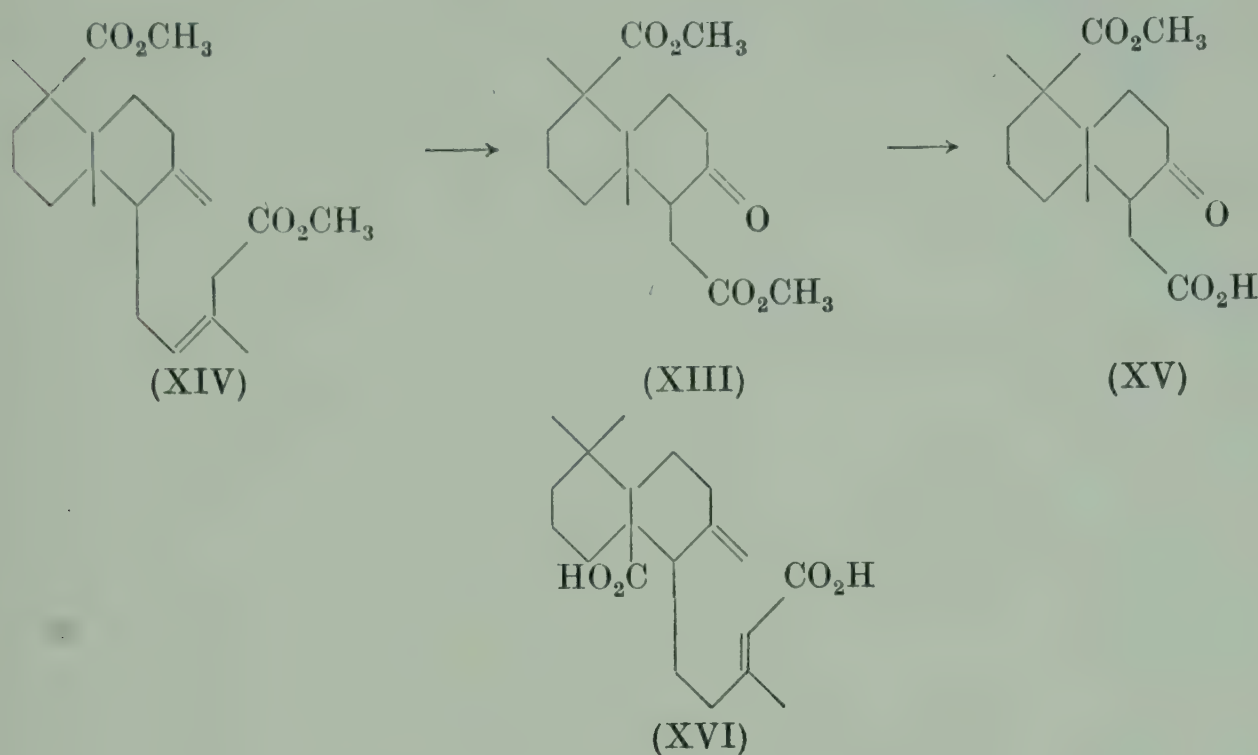
$C_{18}H_{28}O_4$ (VII), m.p. 217–219° and 211–213° (dimorphic), $[\alpha]_D + 70.7^\circ$ (in chloroform) and a very stable *peroxide*, $C_{18}H_{28}O_5$, m.p. 166–167°, $[\alpha]_D^{20} + 171.2^\circ$ (in chloroform), which must be either (VIII) or (IX), since on catalytic hydrogenation followed by oxidation with chromic acid it gave the same diketo-ester (VII). A further product of the oxidation was a tricyclic *keto-ester*, $C_{18}H_{26}O_3$ (X), m.p. 116–117°, $[\alpha]_D^{20} + 48.7^\circ$ (in chloroform), containing an ethylenic linkage in the $\alpha:\beta$ -position to the carbonyl group as proved by its absorption spectrum (λ max. 242 m μ ; $\log \epsilon = 4.26$ in alcohol). This keto ester (X), together with formaldehyde and oxalic acid, formed the main products when dimethyl agathenedicarboxylate was ozonised in carbon tetrachloride solution and the reaction mixture treated with alkali. The cyclisation of the diketo-ester (VII) to the keto-ester (X) occurs with great facility, since even attempts to prepare the disemicarbazone of (VII) resulted in the formation of the same *monosemicarbazone*, m.p. 231–233°, as was obtained from (X).

Proof of the position of the carbonyl group in the keto ester (X) was provided by its reaction with methyl magnesium iodide when, on distillation, the *diene ester*, $C_{19}H_{28}O_2$ (XI), m.p. 73–74°, b.p. 149–150°/0.15 mm., $[\alpha]_D^{20} - 107^\circ$ (in chloroform), λ max. 238 m μ , $\log \epsilon = 4.36$ (in alcohol), was obtained, the position of the ethylenic linkages being deduced from the absorption spectrum and by comparison with abietic acid (p. 385). The ester was dehydrogenated with selenium to pimanthrene (III), whilst with palladised charcoal partial dehydrogenation to the *methyl ester*, $C_{19}H_{26}O_2$ (XII), m.p. 98°, occurred. The presence of an aromatic ring in this acid was deduced from its absorption spectrum.

Esterification of the acid products of the ozonolysis gave, amongst other substances, a *dimethyl ester*, $C_{17}H_{26}O_5$, b.p. 165–166°/0.1 mm., $[\alpha]_D^{20} + 142^\circ$ (in chloroform), yielding on hydrolysis with alkali a *monomethyl ester*, m.p. 177–179°. The dimethyl ester is probably represented by (XIII) resulting from the oxidation of a small percentage of the ester (XIV) possibly present in the dimethyl agathenedicarboxylate. If this is correct then the monomethyl ester would be (XV).

Whilst the experiments outlined above lend strong support to the view that agathenedicarboxylic acid is correctly represented by (I), they are equally well in accord with (XVI), and the evidence

must now be discussed which proves that the position of one of the carboxyl groups is at C₁.

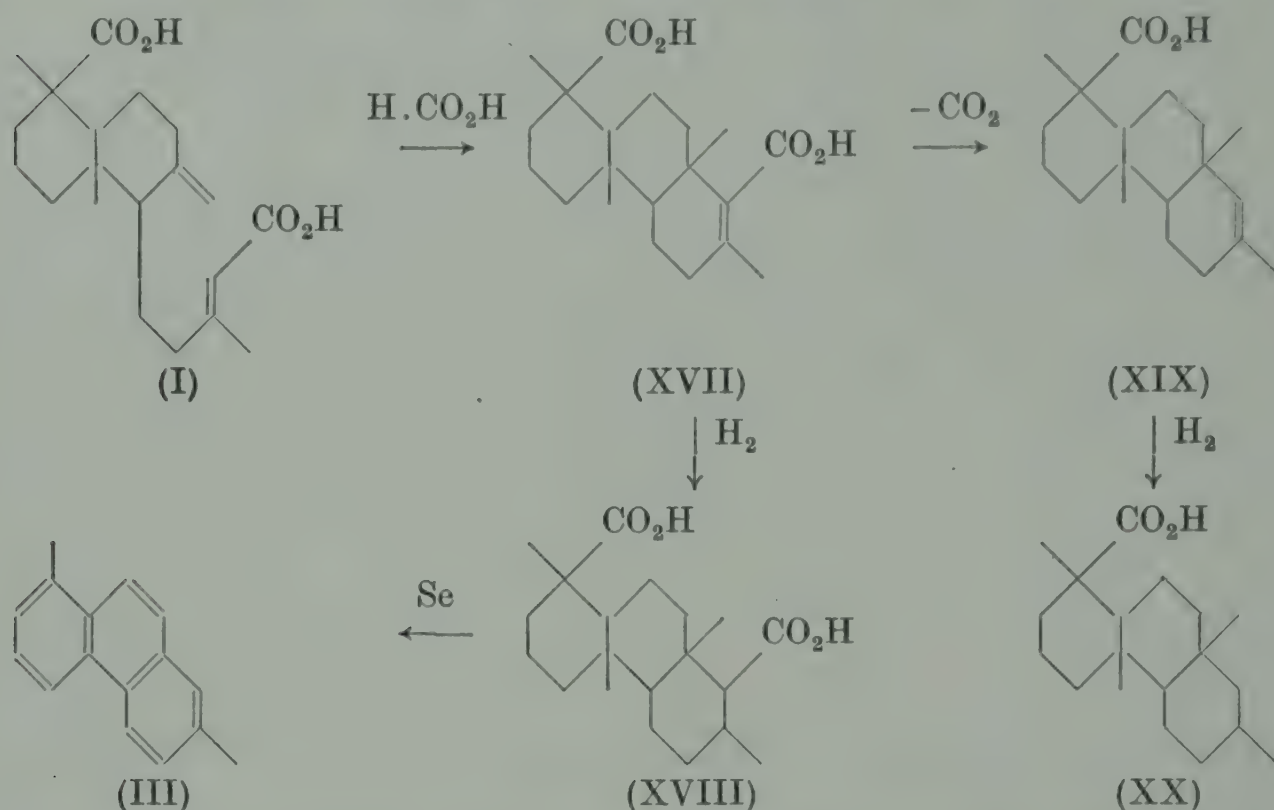


When agathenedicarboxylic acid was digested with formic acid it was isomerised to a tricyclic acid, *isoagathenedicarboxylic acid*, m.p. 287–288° (decomp.), $[\alpha]_D + 12.8^\circ$ (in alcohol), *dimethyl ester*, m.p. 121–122°, $[\alpha]_D + 6.1^\circ$ (in alcohol), *diethyl ester*, m.p. 102–103°, $d_4^{11^\circ} 1.014$, $n_D^{104^\circ} 1.483$, $[\alpha]_D + 9.7^\circ$ (in alcohol). This acid, on the basis of (I), is most probably represented by (XVII). On catalytic hydrogenation it yields *dihydroisoagathenedicarboxylic acid*, C₂₀H₃₂O₄ (XVIII), m.p. 308–310° (decomp.), $[\alpha]_D + 16.0^\circ$ (in alcohol), *dimethyl ester*, m.p. 110–111°, $d_4^{131^\circ} 1.027$, $n_D^{120^\circ} 1.477$, $[\alpha]_D + 9.1^\circ$ (in alcohol), which on dehydrogenation with selenium gave pimanthrene (III), and an unidentified hydrocarbon, unstable *picrate*, m.p. 163–164°.

Like agathenedicarboxylic acid, the *iso*-acid readily loses carbon dioxide when heated above its melting-point to give *isonoragathenemonocarboxylic acid*, C₁₉H₃₀O₂ (XIX), m.p. 177–178°, b.p. 181–184°/0.2 mm., $[\alpha]_D + 2.1^\circ$ (in alcohol), *methyl ester* (XIXa), m.p. 98–99°, $d_4^{112^\circ} 0.978$, $n_D^{102^\circ} 1.4864$, $[\alpha]_D + 2.65^\circ$ (in alcohol), yielding on catalytic hydrogenation *dihydroisonoragathenemonocarboxylic acid* (XX), *methyl ester*, m.p. 80–81°, $d_4^{111^\circ} 0.9714$, $n_D^{102^\circ} 1.4793$, $[\alpha]_D + 35.3^\circ$ (in alcohol).^{*} The more

^{*} Ruzicka and Hosking, *Helv. Chim. Acta*, 1930, 13, 1402.

recent investigations of Ruzicka and Jacobs* and of Ruzicka and Bernold† have shown that neither *isoagathenedicarboxylic acid* nor *isonoragathenemonocarboxylic acid* are homogeneous and this is discussed in greater detail on p. 467.

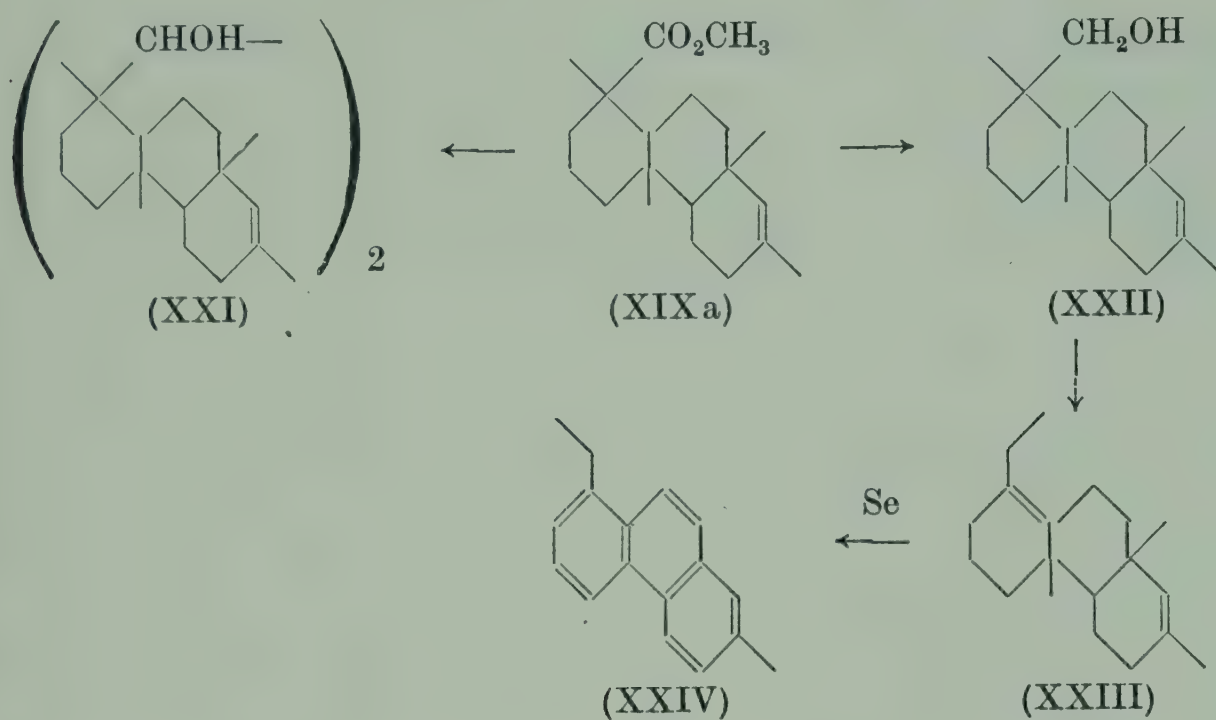


Reduction of methyl *isonoragathenemonocarboxylate* (XIXa), by a modified Bouveault-Blanc method yields, depending upon the conditions used, the *pinacol*, $\text{C}_{38}\text{H}_{62}\text{O}_2$ (XXI), m.p. $222-226^\circ$, or *isonoragathenol*, $\text{C}_{19}\text{H}_{32}\text{O}$ (XXII), m.p. $120-121^\circ$, b.p. $160-161^\circ/0.1$ mm. Dehydration of the alcohol with naphthalene- β -sulphonic acid gave the *hydrocarbon*, $\text{C}_{19}\text{H}_{30}$ (XXIII), b.p. $118-122^\circ/0.2$ mm., $d_4^{20^\circ} 0.9634$, $n_D^{20^\circ} 1.5253$, which on dehydrogenation with selenium afforded 1-ethyl-7-methylphenanthrene (XXIV), identical with the hydrocarbon prepared in a similar way from *d*-pimaric acid (see p. 451). Whilst these experiments provide conclusive evidence of the attachment of one of the carboxyl groups in agathenedicarboxylic acid to C_1 as in (I), additional support was afforded by a similar series of experiments carried out with dimethyl agathenedicarboxylate, dimethyl *isoagathenedicarboxylate* and with methyl *noragathenemonocarboxylate*. Although these experiments proceeded in a somewhat more complicated manner they are of value since, not only do they confirm the attachment of one of the carboxyl groups in

* *Rec. trav. chim.* 1938, **57**, 509.

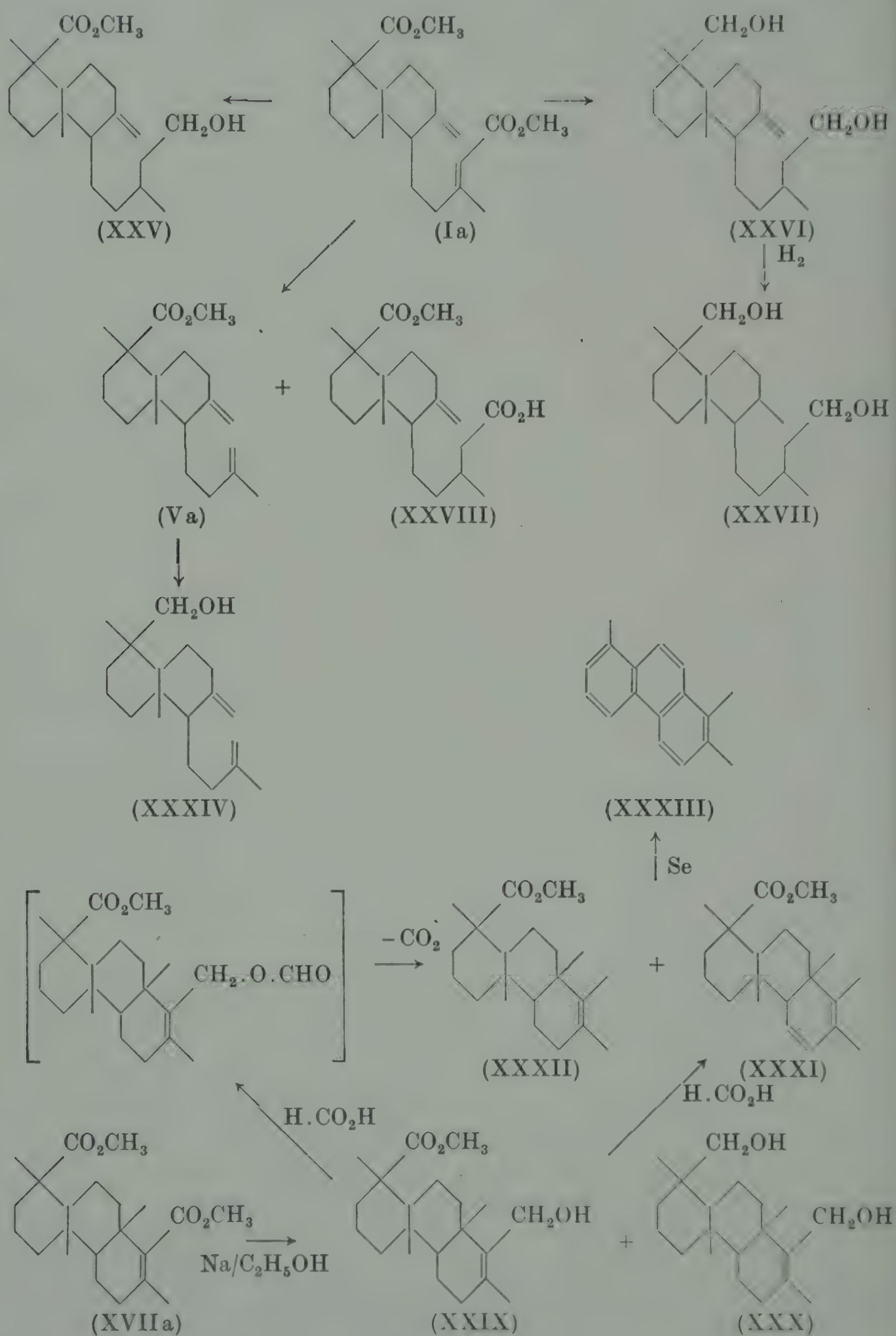
† *Helv. Chim. Acta*, 1941, **24**, 1167.

the C₁ position, but they prove also by chemical means that in agathenedicarboxylic acid one of the carboxyl groups must have an ethylenic linkage in the $\alpha:\beta$ -position. It was found



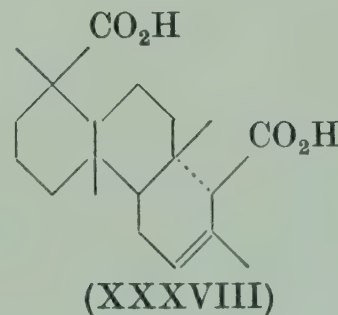
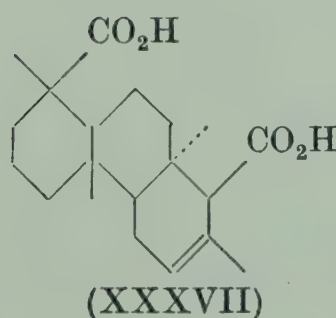
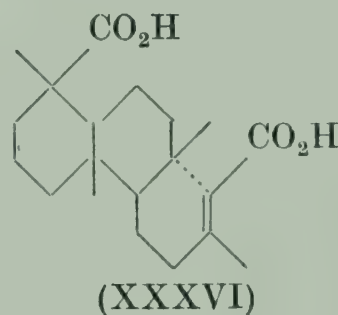
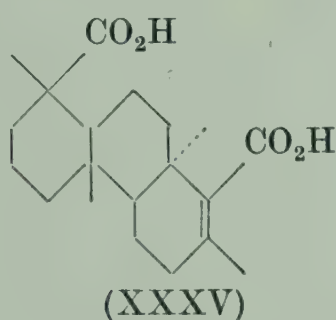
by Ruzicka and Hosking* that the Bouveault-Blanc reduction of dimethyl agathenedicarboxylate (Ia) gave as the main neutral product *methyl hydroxydihydroagathenemonocarboxylate*, C₂₁H₃₆O₃ (XXV) (p. 466), b.p. 193–195°/0.2 mm., $d_4^{15^\circ}$ 1.026, $n_D^{15^\circ}$ 1.5076, accompanied by a small amount of *dihydroxydihydroagathene*, C₂₀H₃₆O₂ (XXVI), m.p. 112–113°, readily reduced by catalytic hydrogenation to the saturated *dihydroxytetrahydroagathene*, C₂₀H₃₈O₂ (XXVII), m.p. 107–108°. The acid products of the reduction lost carbon dioxide on attempted distillation giving a mixture, b.p. 210–212°/0.1 mm., of methyl noragathenemonocarboxylate (Va) and *dihydroagathenedicarboxylic acid monomethyl ester*, C₂₁H₃₂O₄ (XXVIII). The reduction of dimethyl isoagathenedicarboxylate (XVIIa) proceeded in a somewhat similar manner to give a mixture of methyl *hydroxyisoagathenemonocarboxylate*, C₂₁H₃₄O₃ (XXIX), m.p. 125–126°, b.p. 203–205°/0.3 mm., and *dihydroxyisoagathene*, C₂₀H₃₄O₂ (XXX), m.p. 172–173°. Digestion of the hydroxy-ester (XXIX) with formic acid, followed by distillation, gave a mixture of *methyl dehydroisoagathenemonocarboxylate*, C₂₁H₃₂O₂, probably (XXXI) and *methyl isoagathenemonocarboxylate*, C₂₁H₃₄O₂

* *Ibid.* 1931, 14, 203.



(XXXII), b.p. 155–158°/0.4 mm. Dehydrogenation of this mixture with selenium gave 1:7:8-*trimethylphenanthrene* (XXXIII), m.p. 142–143°, *picrate*, m.p. 161–163°. The similar reduction of methyl noragathenemonocarboxylate (Va), which required somewhat vigorous conditions, was shown by Ruzicka and Jacobs* to give the alcohol, *noragathenol*, C₁₉H₃₂O (XXXIV), b.p. 160–161°/0.3 mm., d_4^{51} 0.967, n_D^{51} 1.5077. All these experiments support the view that one of the double bonds of agathenedicarboxylic acid is in the $\alpha:\beta$ -position to one of the carboxyls, and indicate further the sterically protected nature of the C₁ carboxyl (compare p. 470).

It was mentioned above (p. 464) that *isoagathenedicarboxylic acid* and *isonoragathenemonocarboxylic acid* were not homogeneous; the evidence bearing on this will now be discussed. It is obvious that in the case of the former acid there is the possibility of stereoisomerism as represented by (XXXV) and (XXXVI), or of isomerism due to the difference in the position of the ethylenic linkages as in (XXXVII) or (XXXVIII), and an exactly similar reasoning applies for the *isonoragathenemonocarboxylic acid*.

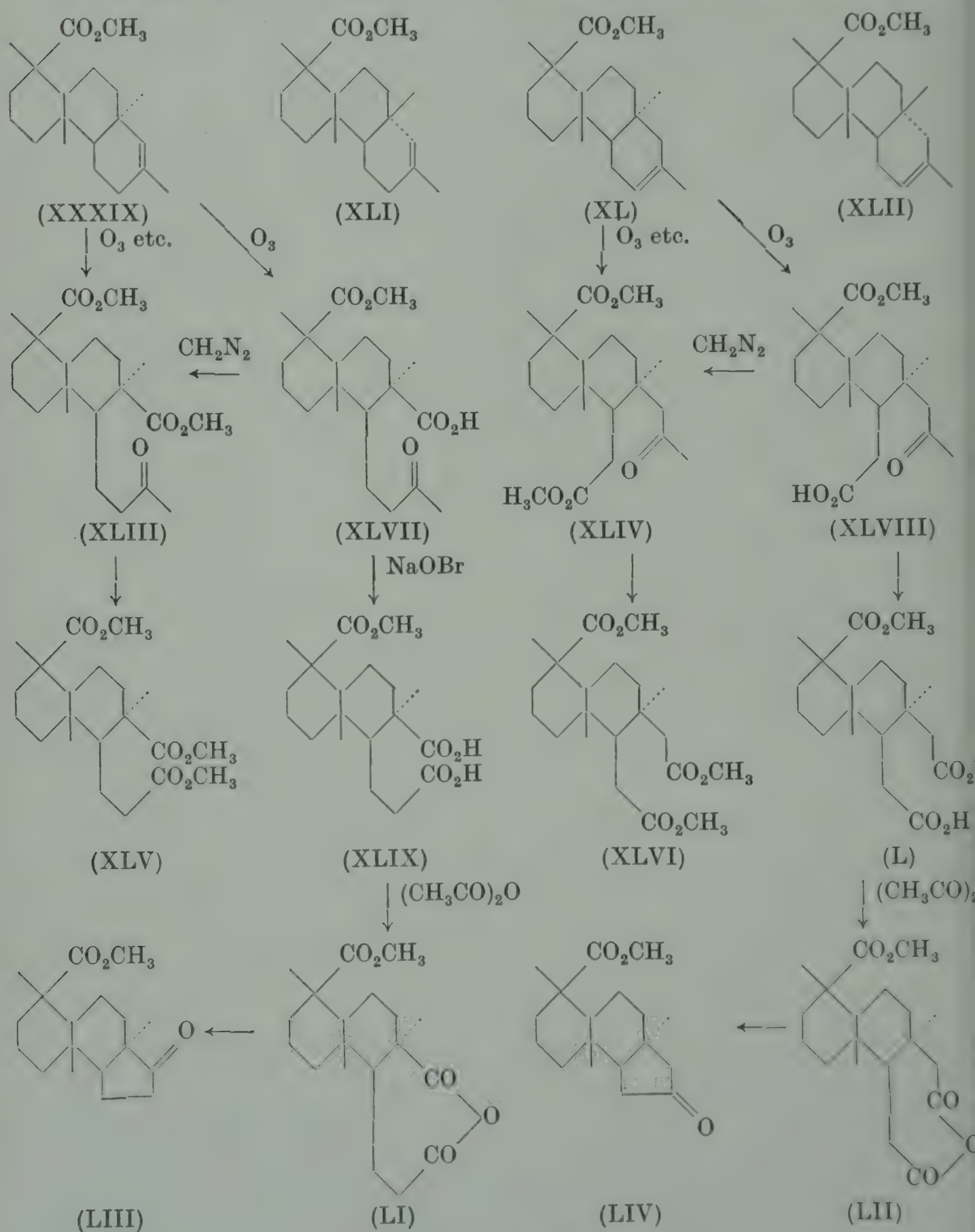


It was found by Ruzicka and Jacobs† that the methyl *isonoragathenemonocarboxylate*, m.p. 98–99°, on fractional crystallisation could be separated into two esters, m.p. 109–110°, $[\alpha]_D + 27.2^\circ$ (in alcohol) and m.p. 92–93°, $[\alpha]_D - 23.2^\circ$ (in alcohol) respectively. It was at the time assumed that these two

* *Rec. trav. chim.* 1938, 57, 509.

† *Loc. cit.*

esters were homogeneous, but the subsequent experiments of Ruzicka and Bernold* showed that the ester, m.p. 109–110°, was probably a mixed crystal of two methyl esters, which for the convenience of exposition may be represented by (XXXIX) and (XL). It was not proved, however, that the mixed crystal



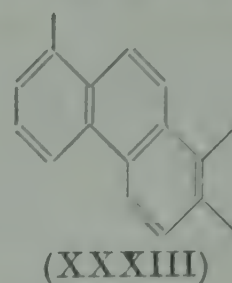
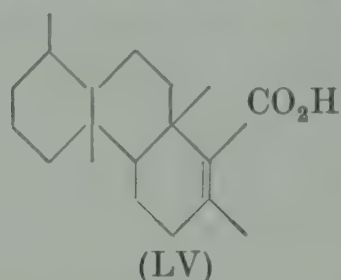
may not consist of the alternatives (XLI) and (XLII), or indeed of any pair from the possible combinations of (XXXIX), (XL), (XLI) and (XLII). On ozonolysis the ester gave a mixture of products which, after esterification with diazomethane, could be separated into a *dimethyl keto-ester*, $C_{21}H_{34}O_5$, m.p. 103–104°, $[\alpha]_D^{20} - 15.0^\circ$ (in chloroform), which may be represented by either (XLIII) or (XLIV) and a mixture of *trimethyl esters*, $C_{21}H_{34}O_6$, b.p. 160–162°/0.2 mm., which may consist of (XLV) and (XLVI). In a second experiment, in which the products were not esterified, two *ketonic acids*, $C_{20}H_{32}O_5$, m.p. 174–175°, $[\alpha]_D^{20} - 9.4^\circ$ (in chloroform), and m.p. 159–160°, $[\alpha]_D^{20} + 1.4^\circ$, which may be represented by (XLVII) and (XLVIII), were obtained. The former acid gave the dimethyl ester, m.p. 103–104°, referred to above, whilst the latter acid gave a *dimethyl ester*, m.p. 70–71°, $[\alpha]_D^{20} + 17.4^\circ$ (in chloroform). It was anticipated that it would be possible to distinguish between (XLIII) and (XLIV) by the difference in their rates of hydrolysis with alkali but this did not prove possible. Oxidation of the keto-acids (XLVII) and (XLVIII) with sodium hypobromite gave two isomeric *monomethyl esters*, $C_{19}H_{30}O_6$, m.p. 229–230°, $[\alpha]_D^{20} + 5.1^\circ$ (in sodium hydroxide solution), and m.p. 167–168°, which may be represented respectively by (XLIX) and (L). The former ester, m.p. 229–230°, gave on digestion with acetic anhydride an *anhydride*, m.p. 206–208°, $[\alpha]_D^{20} + 6.0^\circ$ (in chloroform), (LI) or (LII), and from this a *ketone*, $C_{18}H_{28}O_3$, m.p. 144–145°, $[\alpha]_D^{20} + 173.4^\circ$ (in chloroform), (LIII) or (LIV), was prepared by pyrogenation. These experiments are satisfactorily accounted for by the formulae (XXXIX) to (XLII), inclusive, for methyl *isonoragathenemonocarboxylate*.

The structure of the isomeric ester, m.p. 92–93° (see p. 467), has not been determined. It cannot be (LV), since its absorption spectrum shows no absorption at 220 $m\mu$, nor did the experiments of Ruzicka and Jacobs lead to the isolation of any 1:7:8-trimethylphenanthrene (XXXIII) as would be anticipated if this formula were correct.

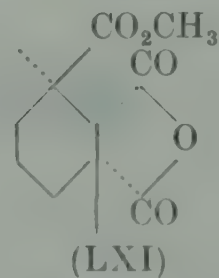
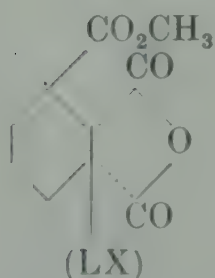
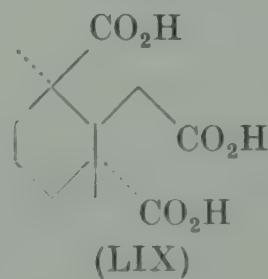
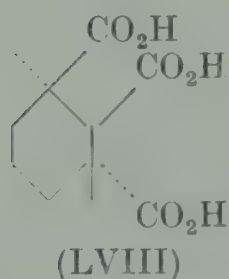
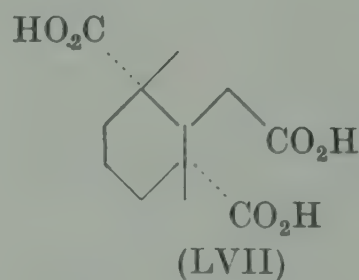
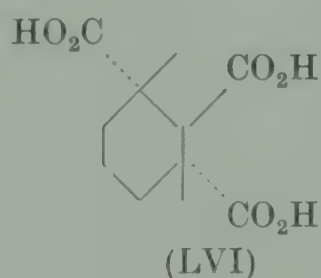
Ruzicka and Bernold* have determined in part the stereochemical configuration of agathenedicarboxylic acid. As mentioned on p. 387 abietic acid gave on energetic oxidation with

* *Ibid.* 1941, **24**, 931.

potassium permanganate, and in other ways, a mixture of two acids, $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_6$, which since they were optically inactive by internal compensation must be (LVI) and (LVII).

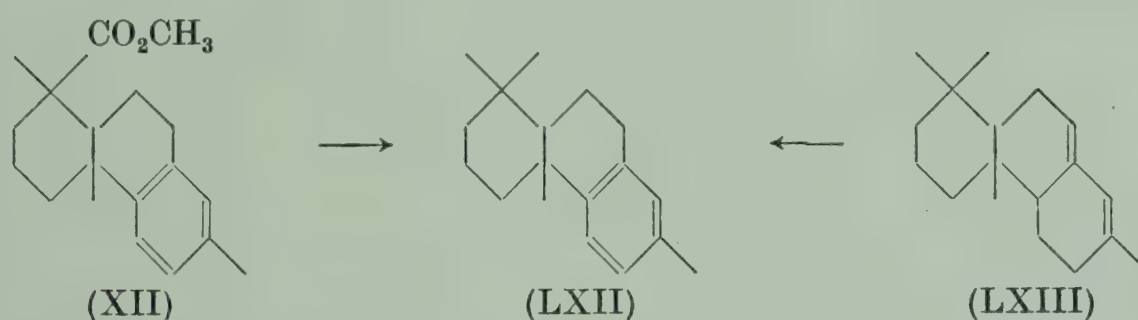


Oxidation of agathenedicarboxylic acid under similar conditions gave after esterification a mixture of *trimethyl esters* having b.p. $127-128^\circ/0.2$ mm., $[\alpha]_D^{20} + 41.1^\circ$ (in methyl alcohol) and analysing as the mixed esters of the similar, homologous tricarboxylic acids, $C_{11}H_{16}O_6$ and $C_{12}H_{18}O_6$. By acid hydrolysis the *monomethyl ester anhydride*, $C_{12}H_{16}O_5$, m.p. $103-104^\circ$, $[\alpha]_D^{20} + 57.9^\circ$, corresponding to the $C_{11}H_{16}O_6$ acid was obtained. Since this mixture of esters is optically active the two acids are most probably represented by (LVIII) and (LIX), and support is lent to this view by the difficulty with which the carbomethoxy group attached to C_1 is hydrolysed in the trimethyl esters of the acids, in the anhydride which is probably (LX), and in dimethyl agathenedicarboxylate.*

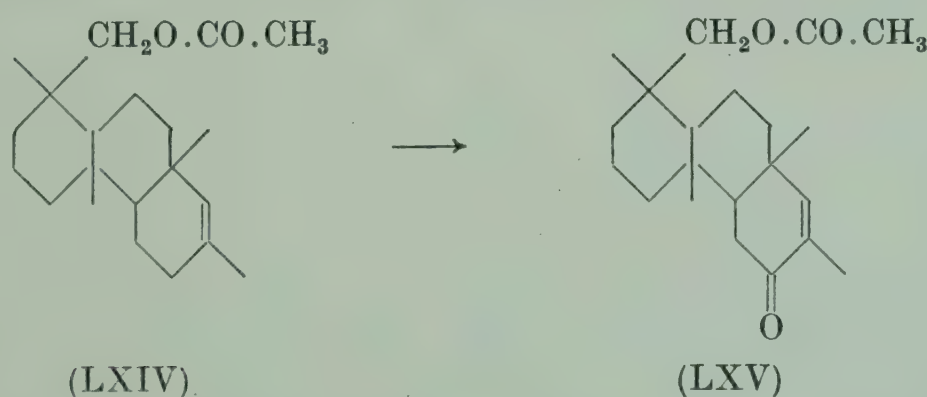


* Ruzicka and Hosking, *Helv. Chim. Acta*, 1931, **14**, 203; Ruzicka and Bernold, *loc. cit.*; compare Campbell and Todd, *J. Amer. C.S.* 1942, **64**, 928.

These experiments do not, of course, determine whether in agathenedicarboxylic acid there is *cis*- or *trans*- fusion of the rings, since the anhydride referred to above can be represented equally by (LX) or (LXI). However the problem has recently been solved by Ruzicka, Zwicky and Jeger* in the following way. The methyl ester (XII), obtained previously from agathenedicarboxylic acid (p. 462), was hydrolysed, the acid converted to the corresponding aldehyde, *semicarbazone*, $C_{19}H_{27}ON_3$, m.p. $226.5-228.5^\circ$, by the Rosenmund method, and the aldehyde semicarbazone reduced by the Wolff-Kishner procedure to the corresponding hydrocarbon (LXII), $C_{18}H_{26}$, b.p. $103-108^\circ/0.04$ mm., $[\alpha]_D + 62^\circ$ (in chloroform). This hydrocarbon was also prepared from (LXIII), a degradation product of manool (p. 353), by dehydrogenation with *N*-bromosuccinimide. Since manool has already been related to abietic acid (see p. 353), which has the A/C ring fusion *trans*, it follows that the ring fusion in agathenedicarboxylic acid must also be *trans*.



The oxidation of *isonoragathenol acetate*, $C_{21}H_{34}O_2$ (LXIV), b.p. $151-153^\circ/0.3$ mm., by selenium dioxide followed by aluminium phenolate in acetone solution, has been studied by



Ruzicka and Bernold.† As expected, an $\alpha:\beta$ -unsaturated *ketone*, $C_{21}H_{32}O_3$ (LXV), m.p. $103-104^\circ$, λ max. $237\text{ m}\mu$, $\log \epsilon = 3.98$, was obtained.

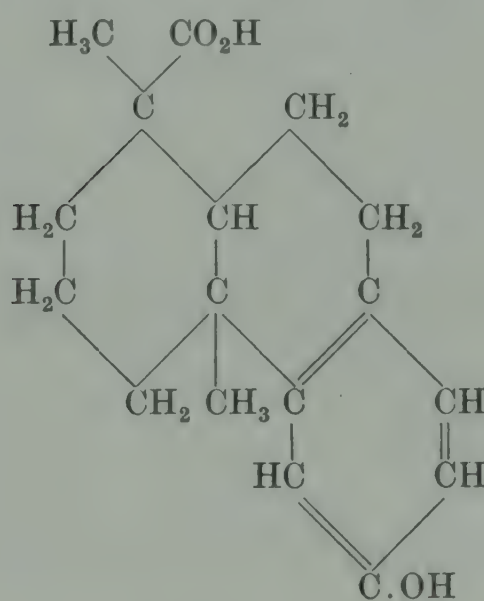
* *Helv. Chim. Acta*, 1948, 31, 2143.

† *Ibid.* 1941, 24, 1167.

According to Ruzicka, Bernold, and Tallichet* dimethyl agathenedicarboxylate reacts with maleic anhydride by heating under pressure to give an adduct, $C_{28}H_{42}O_8$, b.p. 219–222°/0.1 mm., $[\alpha]_D^{20} + 28.53^\circ$ (in chloroform), but the nature of this substance has not been determined.

C. HYDROXY MONOCARBOXYLIC ACID

PODOCARPIC ACID



Although podocarpic acid cannot be classified as a member of the diterpenoid resin acids some account of its chemistry is given here, because its very close relationship to dehydroabietic acid (p. 413) and ferruginol (p. 355) makes it a key compound in the exposition of the chemistry of these substances.

Podocarpic acid, $C_{17}H_{22}O_3$ (I), m.p. 193°, $[\alpha]_{5461} + 165^\circ$, $[\alpha]_{5780} + 144^\circ$ (both in alcohol), was first isolated by Oudemans† from the resin of *Podocarpus cupressina*, a tree growing in Java and New Zealand. It was obtained later by Easterfield and Aston‡ from the resin of *P. dacrydioides* and also from *Dacrydium cupressinum*,§ both of which occur in New Zealand.|| The isolation of podocarpic acid from all three of these sources has been described by Sherwood and Short.¶

* *Helv. Chim. Acta*, 1941, **24**, 223.

† *Ber.* 1873, **6**, 1122, 1125; *Annalen*, 1873, **170**, 214; *J. pr. Chem.* 1874 [i], **9**, 385.

‡ *Trans. New Zealand Inst.* 1910, **42**, 53.

§ *Ibid.* 1911, **43**, 53.

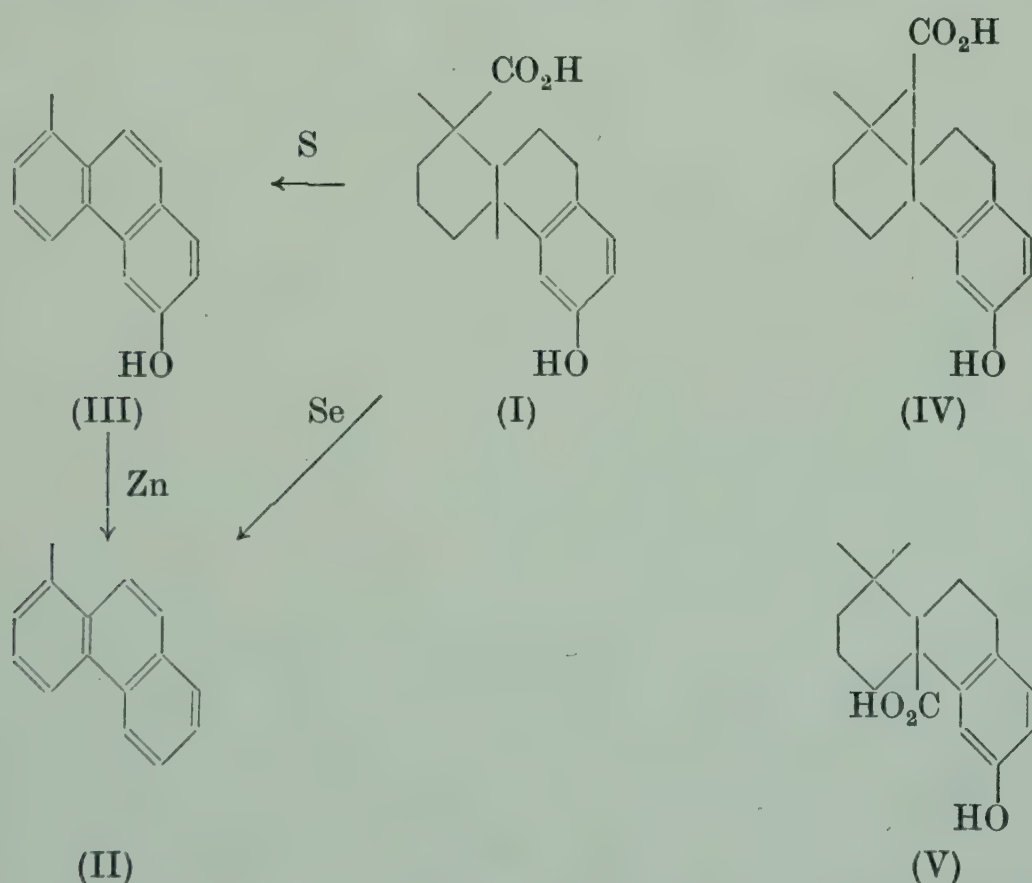
|| Compare Easterfield and Aston, *ibid.* 1904, **36**, 483.

¶ *J.C.S.* 1938, p. 1006; compare Sherwood and Short, *Rep. Australian Assoc. Adv. Sci.* 1933, **21**, 38.

The presence of a phenolic hydroxyl group in podocarpic acid was recognised by Oudemans, who showed that the acid was very readily nitrated with dilute nitric acid to give a *mononitro* derivative, m.p. 205° , or a *dinitro* derivative, m.p. 203° , depending on the conditions of reaction, and was equally readily sulphonated to furnish a *monosulphonic acid*. Furthermore, whilst the acid itself was only monobasic, as shown by salt formation, the phenolic hydroxyl in the nitro derivatives was sufficiently acidic to cause dibasic behaviour.

The carbon skeleton of podocarpic acid has been determined by dehydrogenation with palladised charcoal or selenium, when 1-methylphenanthrene (II) and 6-hydroxy-1-methylphenanthrene (III), m.p. 161° ; *picrate*, m.p. 182° , *acetate*, m.p. $118-119^{\circ}$, *benzoate*, m.p. 147° , *methyl ether*, m.p. $87-87.5^{\circ}$, were obtained. Dehydrogenation with sulphur afforded only the phenol (III), which was converted to (II) by distillation with zinc dust.* This evidence as to the structure of podocarpic acid is satisfactorily accounted for by the formula (I), but the two alternative representations (IV) and (V) have also received consideration.

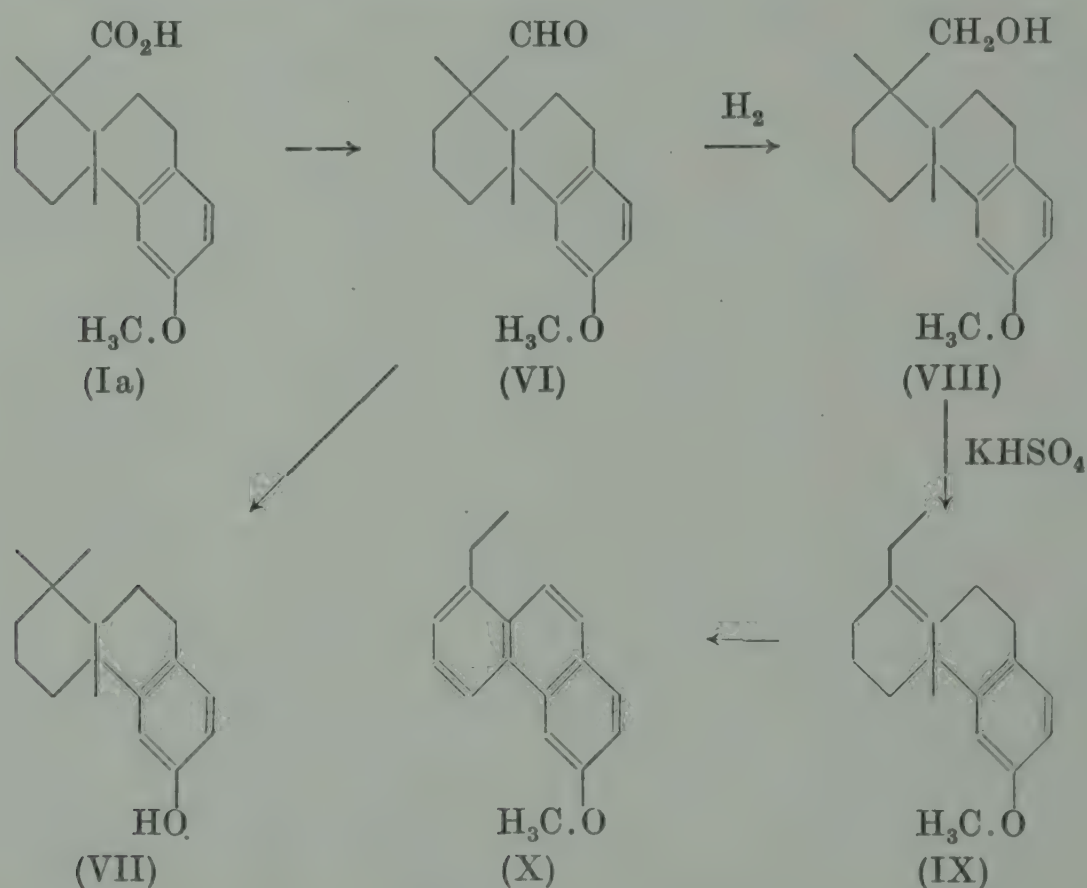
That (I) correctly represents the acid has been proved by Campbell and Todd.† Podocarpic acid methyl ether (Ia) (see



* Sherwood and Short, *loc. cit.*; Plimmer and Short, *ibid.* 1938, p. 694.

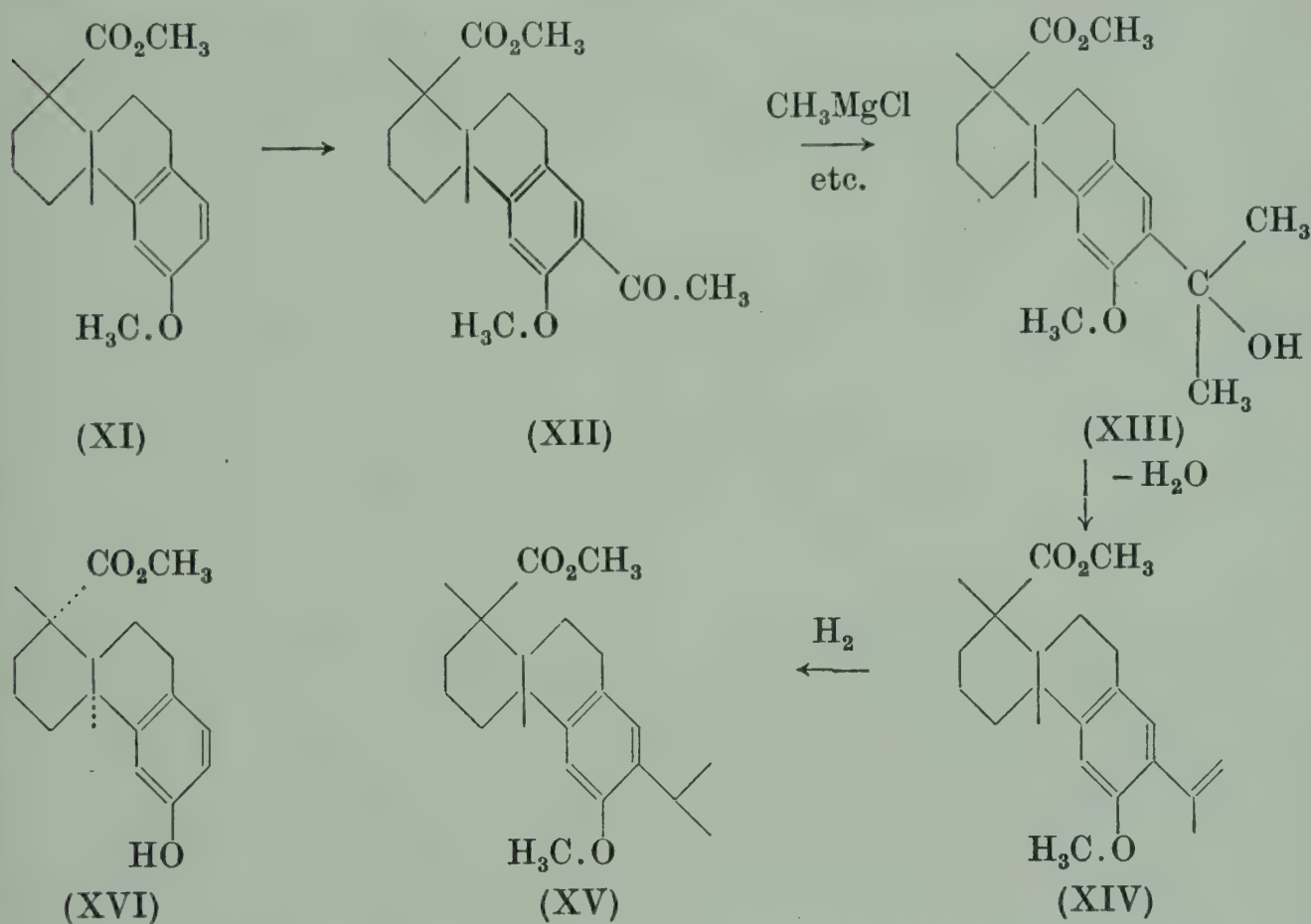
† *J. Amer. C.S.* 1942, **64**, 928.

below) was reduced by the Rosenmund method to *methoxypodocarpinal* (VI), m.p. 133–135°, *semicarbazone*, m.p. 205° decomp., the latter being further reduced by the Kishner-Wolff method to *hydroxypodocarpane* (VII), m.p. 140.5–141.5°. By high pressure hydrogenation using a copper chromite catalyst the aldehyde (VI) was reduced to *methoxypodocarpinol* (VIII), m.p. 90–91.5°. On dehydration of the alcohol with potassium bisulphate the *methyl ether* (IX) was obtained and this, after catalytic hydrogenation, was dehydrogenated with selenium to 1-ethyl-6-methoxyphenanthrene (X), *picrate*, m.p. 126–126.5°, *styphnate*, m.p. 139–140.5°, *trinitrobenzene* adduct, m.p. 137–137.5°, identical with a synthetic specimen.



Methyl podocarpate methyl ether (XI) undergoes a smooth Friedel-Crafts reaction with acetyl chloride to furnish the *ketone* (XII), m.p. 119–119.5°, $[\alpha]_{\text{H}_g}^{25^\circ} + 142^\circ$ (in alcohol) (*oxime*, m.p. 190–193°), which on treatment with methyl magnesium chloride gives the tertiary *alcohol* (XIII), m.p. 148–150°, $[\alpha]_{\text{H}_g}^{25^\circ} + 119^\circ$ (in alcohol), dehydrated by acetic acid to the *isopropenyl* compound (XIV), m.p. 120.5–121.5°, $[\alpha]_{\text{H}_g}^{25^\circ} + 136^\circ$ (in alcohol). The *isopropenyl* group of (XIV) was easily reduced by catalytic hydrogenation to the corresponding *isopropyl* compound (XV), m.p. 109–109.5°, $[\alpha]_{\text{H}_g}^{25^\circ} + 124^\circ$ (in alcohol), which was found not

to be identical with the isomeric *methyl 6-methoxydehydroabietate* (see p. 423). This implies that the configuration of the carboxyl group in podocarpic acid must be epimeric to that in abietic acid, and this view is supported by the marked steric hindrance to hydrolysis of methyl podocarpate and its derivatives as compared with the esters of abietic acid. The final proof that this conclusion is correct and also of the position of the *isopropyl* group in (XV) was afforded by the synthesis of ferruginol described on p. 356. The stereostructure of podocarpic acid can be partially expressed therefore by the formula (XVI).

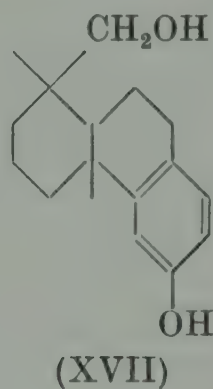


Podocarpic acid can be characterised by the preparation of an *acetate*, m.p. 173–176°, a *methyl ester*, m.p. 208° (*benzoate*, m.p. 143.5°), an *ethyl ester*, m.p. 161°, a *p-nitrobenzyl ester*, m.p. 204° and a *methyl ether* (Ia), m.p. 158° (methyl ester (XI), m.p. 128°). As would be expected from the presence of a phenolic hydroxyl group it gives a green colour with ferric chloride and couples with diazotised sulphanilic acid. Complex products, including *p*-cresol and the phenol (III), are obtained by the dry distillation of the calcium salt of podocarpic acid.* When podocarpic acid is subjected to the Schmidt reaction with hydrazoic acid a primary

* Oudemans, *loc. cit.*; Sherwood and Short, *loc. cit.*

amine, $C_{16}H_{23}ON$, sulphate, m.p. 279° decomp., is obtained in which the carboxyl group of podocarpic acid has been replaced by an amino group.*

Podocarpic acid is readily reduced by lithium aluminium hydride to podocarpinol (XVII), $C_{17}H_{24}O_2$, m.p. $178-179^\circ$. Similar reduction of podocarpic acid chloride methyl ether and of methyl podocarpate methyl ether gives methoxypodocarpinol (VIII),† whilst methyl 7-isopropylpodocarpate methyl ether affords 7-isopropylpodocarpinol methyl ether, $C_{21}H_{32}O_2$, m.p. $83-85^\circ$, hydrolysed to 7-isopropylpodocarpinol, $C_{20}H_{30}O_2$, m.p. $185.4-186.4^\circ$.‡ Podocarpinol has also been prepared from podocarpic acid acetate by the same method as used by Campbell and Todd for the preparation of methoxypodocarpinol (see above).§



Experiments leading to the synthesis of *rac.*-podocarpic acid or a racemic stereoisomer thereof have recently been recorded by Haworth and Moore.||

D. ACIDS OF UNKNOWN CONSTITUTION

CATIVIC ACID

The oleo-resin from *Prioria copaifera* Griseb. (cativa tree) contains the interesting resin acid, *cativic acid*, $C_{20}H_{34}O_2$, b.p. $194-195^\circ/1$ mm., $d_{23}^{23^\circ} 0.9987$, $n_D^{24^\circ} 1.5090$, which occurs in the resin both in the free state and esterified with the corresponding

* Briggs, De Ath and Ellis, *J.C.S.* 1942, p. 61.

† Zeiss, Slimowicz and Pasternak, *J. Amer. C.S.* 1948, **70**, 1981.

‡ Buizer, Karmowsky and Bywater, *ibid.* 1950, **72**, 3800.

§ Brandt and Ross, *Nature*, 1948, **161**, 892.

|| *J.C.S.* 1946, p. 633; compare Bhattacharyya, *Sci. and Culture*, 1942, **8**, 274.

primary alcohol, *cativyl alcohol*, $C_{20}H_{36}O$, b.p. $208.5-209.5/4.5$ mm., *acetate*, b.p. $191^{\circ}/2.5$ mm.* Although cativic acid is probably diterpenoid it differs from abietic and related acids in that its carboxyl group is readily esterified to give, for example, the *methyl ester*, $C_{21}H_{36}O_2$, b.p. $200^{\circ}/1$ mm., $d_{21}^{21^{\circ}} 0.985$. Various other esters have been reported.† Oxidation with potassium permanganate affords *dihydroxycativic acid*, $C_{20}H_{36}O_4$, m.p. 158° , *methyl ester*, m.p. 64° .

MIROPINIC ACID

Brandt and Neubauer‡ have isolated two isomeric acids, *miropinic acid*, $C_{20}H_{30}O_2$, m.p. 160° , $[\alpha]_D^{16^{\circ}} - 3.6^{\circ}$ (in 1:1 alcohol-chloroform), *methyl ester*, b.p. $148^{\circ}/0.3$ mm., $n_D^{20^{\circ}} 1.5203$ and *isomiropinic acid*, m.p. 284° , $[\alpha]_D^{17^{\circ}} + 21.2^{\circ}$ (in dioxan) from the resin exuded by the miro tree (*Podocarpus ferruginea*), endemic to New Zealand. Miropinic acid is possibly identical with *cryptopimaric acid*, isolated by Keimatsu, Ishiguro and Fukuri§ from *Cryptomeria japonica* and with an acid obtained from *Dacrydium biforme* and *Dacrydium Kirkii*,|| and it has been shown to be identical with *iso-d-pimaric acid* (see p. 457).¶

VOUACAPENIC ACID

The heart wood of *Vouacapoua americana* Aubl. contains the *methyl ester*, $C_{21}H_{30}O_3$, m.p. 105° , b.p. $185^{\circ}/0.5$ mm., $[\alpha]_D^{18^{\circ}} + 101^{\circ}$ (in carbon tetrachloride), of vouacapenic acid, $C_{20}H_{28}O_3$, m.p. $226-229^{\circ}$, $[\alpha]_D + 108^{\circ}$ (in carbon tetrachloride). The carboxyl group is strongly hindered sterically and drastic conditions are needed for the hydrolysis. Vouacapenic acid possesses two ethylenic linkages as is shown by per-acid titration and by catalytic hydrogenation of the methyl ester to give *tetrahydrovouacapenic acid methyl ester*, $C_{21}H_{34}O_3$, m.p. $129-131.5^{\circ}$, $[\alpha]_D + 45^{\circ}$ (in carbon tetrachloride). The nature of the third oxygen

* Kalman, *J. Amer. C.S.* 1938, **60**, 1423.

† *Idem*, loc. cit.

‡ *J.C.S.* 1940, p. 683.

§ *J. Pharm. Soc. Japan*, 1937, **57**, 69.

|| Hosking and Brandt, *Ber.* 1935, **68**, 1313; Hosking, *New Zealand J. Sci. Tech.* 1937, **19**, 208.

¶ Brossi and Jeger, *Helv. Chim. Acta*, 1950, **33**, 722.

atom has not been ascertained with certainty but it is probably present as an ether grouping because, whilst tetrahydrovouacapenic acid methyl ester has no hydroxyl group, the by-product in the catalytic hydrogenation, *hexahydrovouacapenic acid methyl ester*, $C_{21}H_{36}O_3$, b.p. $190^{\circ}/0.8$ mm., does show hydroxyl reactivity. Vouacapenic acid is almost certainly a member of the diterpenoid resin acid family.*

* Spoelstra, *Rec. trav. Chim.* 1930, **49**, 226.

CHAPTER VI

LACTONE

MARRUBIIN

The diterpenoid lactone, marrubiin, $C_{20}H_{28}O_4$, m.p. 158° , which constitutes the bitter principle of the horehound (*Marrubium vulgare* L.) was first described by Harms.* Although it was subsequently examined by Kroymeyer,[†] Hertel,[‡] Morrison,[§] Matusow^{||} and Gordin,[¶] it was first obtained pure by Mercier and Mercier.** The chemistry of marrubiin has been investigated by Gordin,^{††} Lawson and Eustice^{‡‡} and by Hollis, Richards and Robertson.^{§§} The presence of a lactone ring was established by its facile hydrolysis by alkali to the monobasic hydroxy-acid, *marrubic acid*, $C_{20}H_{30}O_5$, m.p. 205° decomp., *methyl ester*, m.p. 85° , *ethyl ester*, m.p. 88° , *acetate*, m.p. 112° . On catalytic hydrogenation marrubiin was converted to *tetrahydromarrubiin*, $C_{20}H_{32}O_4$, m.p. 134° , hydrolysed to *tetrahydromarrubic acid*, $C_{20}H_{34}O_5$, m.p. 187° , *ethyl ester*, m.p. 95° , which was also prepared directly by the reduction of marrubic acid. Marrubiin probably contains a tertiary hydroxyl group, since it was dehydrated by the action of either phosphorus trichloride or thionyl chloride to *anhydromarrubiin*, $C_{20}H_{26}O_3$, m.p. 98° , which yielded on hydrolysis *anhydromarrubic acid*, $C_{20}H_{28}O_4$, m.p. 152° . Anhydromarrubiin was reduced catalytically to the saturated lactone, *hexahydroanhydromarrubiin*, $C_{20}H_{32}O_3$, m.p. 106° , from which the corresponding saturated acid, *hexahydroanhydromarrubic acid*, $C_{20}H_{34}O_4$, m.p. 210° , was obtained on hydrolysis. This conclusion, that marrubiin contained a tertiary hydroxyl group, was supported by the observation that tetrahydromarrubiin was similarly dehydrated by treatment with hydrogen chloride to give *anhydrotetrahydromarrubiin*, $C_{20}H_{30}O_3$, m.p. 224° , which furnished on catalytic reduction a saturated lactone, $C_{20}H_{32}O_3$,

* *Arch. Pharm.* 1842, **83**, 144; 1851, **116**, 141.

† *Ibid.* 1849, **108**, 258.

§ *Ibid.* 1890, **62**, 327.

¶ *J. Amer. C.S.* 1908, **30**, 265.

†† *Loc. cit.*

§§ *Nature*, 1939, **143**, 604.

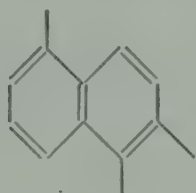
‡ *Amer. J. Pharm.* 1890, **62**, 273.

|| *Ibid.* 1897, **69**, 201.

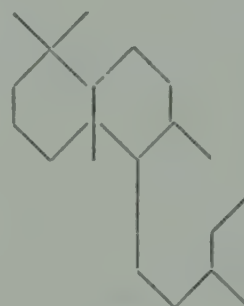
** *Compt. rend.* 1932, **195**, 1102.

‡‡ *J.C.S.* 1939, p. 587.

m.p. 89° , probably stereoisomeric with the hexahydroanhydromarrubiin mentioned above. The remaining oxygen atom present in marrubiin is probably in an oxide ring, but this has not been proved directly. These experiments show that marrubiin must possess a bicyclic carbon skeleton, and this is supported by its dehydrogenation with selenium to 1:5:6-trimethylnaphthalene (I). Marrubiin is probably therefore related to sclareol (p. 360), manoyl oxide (p. 368) and agathenedicarboxylic acid (p. 459) and may have the carbon skeleton (II).



(I)



(II)

ADDENDA

THE USE OF RAMAN AND INFRA-RED SPECTRA FOR THE DETERMINATION OF THE STRUCTURE OF TERPENES

(VOL. I, p. 4)

During the last few years, Raman spectra have been increasingly used in many branches of organic chemistry, and, with the continued accumulation of data and the improvement in techniques, many of the earlier uncertainties have disappeared. Considerable advances have also been made in the measurement and interpretation of infra-red spectra. It is still doubtful, however, to what extent reliance may be placed upon the results obtained with certain terpenes, partly because the physical investigators themselves do not always agree on the precise interpretations of the spectra, and also because the results are often at variance with the chemical evidence.*

The most recent studies on the *isopropenyl-isopropylidene* controversy have been concerned with the examination of the infra-red spectra of several specimens of geraniol, citronellol, citronellal, etc.,[†] and are interpreted to indicate that the materials consist exclusively, or very nearly so, of the *isopropylidene* modifications, as had already been deduced on the basis of Raman spectra.[‡] Unfortunately, no chemical evidence on these particular specimens was recorded, but in view of the earlier oxidation experiments, which always showed the presence of an appreciable amount of the *isopropenyl* form, it is concluded that oxidation does not provide an unequivocal proof of structure.

Whilst it is recognised that the ozonisation of unsaturated compounds can result in excessive degradation, particularly

* Reference is made later (p. 502) to the conflicting views of Naves and Ruzicka with regard to the relative accuracy of Raman and infra-red determinations, and to the discrepancies between their conclusions as to the main component of natural irone.

† Thompson and Whiffen, *J.C.S.* 1948, p. 1412; Carroll, Mason, Thompson and Wood, *ibid.* 1950, p. 3457; Barnard, Bateman, Harding, Koch, Sheppard and Sutherland, *J.C.S.* 1950, p. 915.

‡ Compare Naves, *Perfum. essent. Oil Rec.* 1949, **40**, 40; *Bull. Soc. Chim.*, 1951, [v], **18**, 506.

when rather drastic methods are used in working up the reaction products,* it would be somewhat surprising if this were the sole explanation of the present difficulties, particularly since many pure *isopropylidene* compounds are known which give only acetone, and not more than a trace of formaldehyde, on ozonolysis under the usual conditions. For example, Caldwell and Jones[†] have shown that crystalline geranamide and also tetrahydrogeranamide on ozonolysis both give about 3 per cent of formaldehyde; this small amount is evidently the result of abnormal oxidation, but the amount of formaldehyde obtained from certain samples of citronellol, etc., often amounts to 20 per cent or more.

The abnormal results could be explained by tautomerism:



on the assumptions (i) that the normal equilibrium is very largely on the *isopropylidene* side (at least 99 per cent); and (ii) that the *isopropenyl* form reacts with ozone very much faster than the other. On theoretical grounds, however, the mobility of such a system would be very low in the absence of any of the usual activating groups.

It is clear that this problem has reached a very interesting position, and that further physical and chemical investigations are necessary before the final solution can be achieved.

DIHYDROMYRCENE

(Vol. I, p. 9)

The addition of thiolacetic acid to dihydromyrcene gives a mixture of mono- and di- addition products.[‡]

* See, for example, Ziegler, Hechelhammer, Wagner and Wilms. *Annalen*, 1950, 567, 99.

† *J.C.S.* 1946, p. 599.

‡ Cunneen, *J.C.S.* 1947, p. 134.

OCIMENE

(Vol. I, p. 19)

A hydrocarbon named β -ocimene has been isolated by Crabalona* from lavender oil. It has b.p. 51–52°/6.5 mm., $d_4^{20^\circ}$ 0.8000, $n_D^{20^\circ}$ 1.4862, $\alpha_D \pm 0^\circ$, reacts with six atoms of bromine, and gives an adduct with maleic anhydride (free acid, m.p. 163°).

CITRONELLOL

(Vol. I, p. 26)

The absorption spectrum of citronellol in alcohol has been recorded by Naves and Ardizio† and does not agree with earlier results.

When citronellol is hydrogenated over nickel, it gives a mixture of dihydrocitronellol, dihydrocitril, and hydrocarbons.‡ Over platinum, however, in ethyl acetate solution at 60°, it gives the decanol only; this provides a possible method for the identification of citronellol in the presence of geraniol or nerol, which under these conditions give dimethyloctane.§

Oxidation of citronellol to citronellal, by a modified Oppenauer process, is described by Lauchenauer and Schinz.||

GERANIOL

(Vol. I, p. 40)

The absorption spectrum of geraniol in alcohol has been recorded by Naves and Ardizio¶ and differs from earlier observations.

When geraniol is passed over copper at 165–250°, very little citral is obtained, the main product being citronellal, possibly formed by recombination of citral with the liberated hydrogen.**

* *Bull. Soc. chim.* 1948, p. 384.

† *Helv. Chim. Acta*, 1948, **31**, 1240.

‡ Ishimura and Tamira, *Bull. Chem. Soc. Japan*, 1943, **18**, 194.

§ Naves, *Helv. Chim. Acta*, 1946, **29**, 1447.

|| *Ibid.* 1949, **32**, 1265.

¶ *Ibid.* 1948, **31**, 1240.

** Alquier, *Amer. Chem. Abstr.* 1948, **42**, 3311.

Hydrogenation of geraniol in ethyl acetate solution, over platinum at 60°, gives dimethyloctane, in contrast to the reduction of citronellol under similar conditions (compare p. 483).^{*}

Under the normal Oppenauer conditions, the oxidation of geraniol gives *pseudo-ionone*, the initially formed citral condensing with the acetone used as oxidant.[†] By a modified procedure, however, in which anisaldehyde or cinnamaldehyde is used as hydrogen acceptor, this complication is avoided, and geraniol then yields citral.[‡]

Treatment of geranyl chloride with sodium or potassium geranoxide gives *digeranyl ether*, b.p. 132°/0.1 mm., n_D^{20} 1.4846.[§]

A synthesis of squalene, by reaction of geranyl acetone with tetramethylene dibromide and magnesium, has been described by Schmitt.^{||}

LAVANDULOL

(Vol. I, p. 54)

The original synthesis of lavandulol was not entirely satisfactory, since the product was probably not homogeneous. More recently, Schinz and Schäppi[¶] have reported an improved method in which isoprene hydrobromide (I) was condensed with ethyl acetoacetate to give the keto-ester (II); after protection of the keto-group by formation of the ethylene acetal (III), reduction by the Bouveault-Blanc method gave the corresponding primary alcohol (IV), and thence, by hydrolysis of the acetal, the keto-alcohol (V) was obtained. This substance (Vol. I, p. 55, formula III) had previously been used in the original synthesis, but, having then been prepared by condensation of methyl heptenone with formaldehyde, it was probably contaminated with the isomeric hydroxy-ketone formed by reaction of the formaldehyde with the methyl, rather than the methylene, group adjacent to the carbonyl group. Treatment of the pure keto-alcohol (V) with methylmagnesium iodide to give (VI), followed by dehydration^{**}

* Naves, *Helv. Chim. Acta*, 1946, **29**, 1450.

† Compare Yamashita and Honjo, *J.C.S. Japan*, 1942, **63**, 1335.

‡ Lauchenauer and Schinz, *Helv. Chim. Acta*, 1949, **32**, 1265.

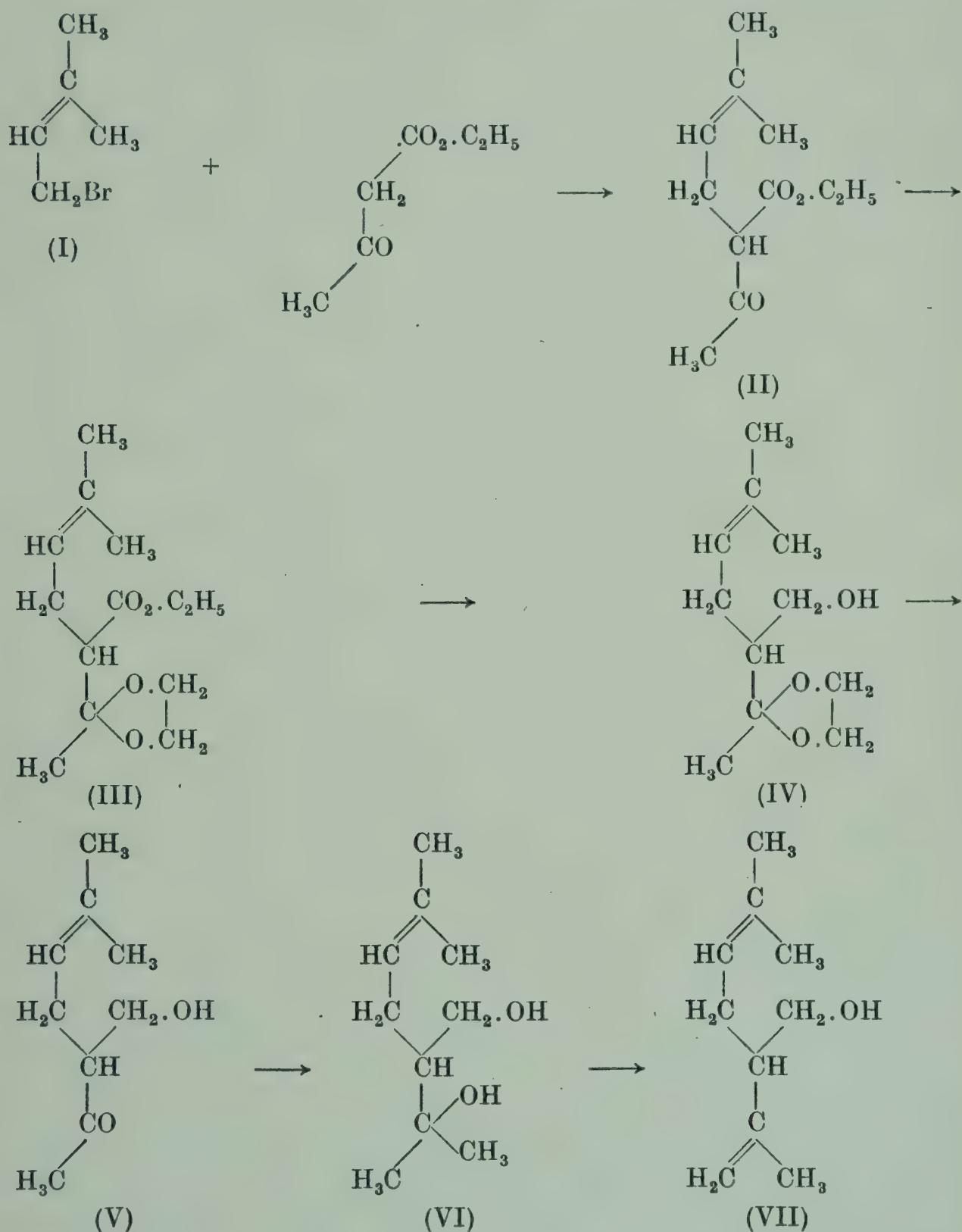
§ Naylor, *J.C.S.* 1949, p. 2724.

|| *Annalen*, 1941, **547**, 115.

¶ *Helv. Chim. Acta*, 1947, **30**, 1483.

** Pyrolysis of the diacetate of (VI) to lavandulyl acetate, followed by hydrolysis was found to be the most satisfactory method, since direct dehydration gave undesirable by-products.

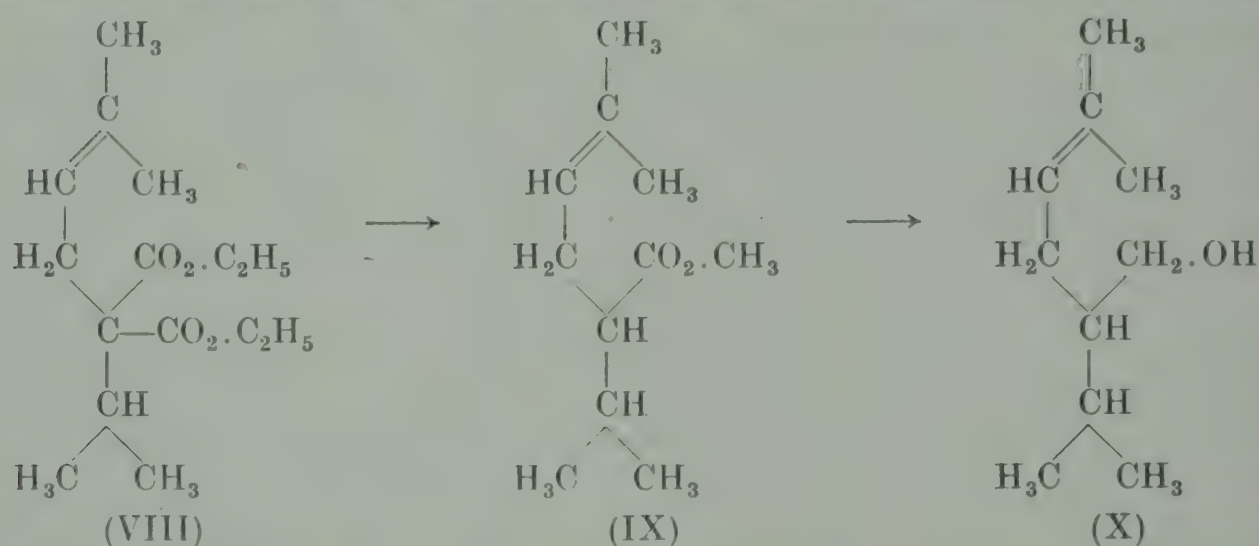
gave *dl*-lavandulol (VII), b.p. 100–101°/16 mm., $d_4^{17^\circ}$ 0.8794, $n_D^{17^\circ}$ 1.4705. The *allophanate* had m.p. 117–118°, which was unchanged on admixture with the *allophanate*, m.p. 117–118°, of the natural *l*-lavandulol. The 3:5-*dinitrobenzoate* had m.p. 75°;



a mixed m.p. with the *l*-derivative, m.p. 59–60°, was 71–73°; a mixed m.p. with the 3:5-dinitrobenzoate of synthetic *iso*-lavandulol, m.p. 74–75°, was depressed by 15°. Hydrogenation of the synthetic lavandulyl acetate gave the tetrahydro-

derivative, which on hydrolysis gave *dl-tetrahydrolavandulol* (*allophanate*, m.p. 99–100°), identical with that previously obtained by reduction of *isolavandulol* (compare Vol. I, p. 56).

Simon, Kaufmann, and Schinz* have described a synthesis of *dihydrolavandulol* in which isoprene hydrobromide was condensed with ethyl isopropylmalonate to give (VIII). Decarboxylation of the corresponding dicarboxylic acid, followed by esterification with diazomethane gave the *methyl ester* (IX), reduction of which, by the Bouveault-Blanc method, gave *dl-dihydrolavandulol* (X), b.p. 95°/12 mm., d_4^{18} 0.8603, n_D^{18} 1.4572 (*allophanate*, m.p. 121–122°). On ozonisation it gave much



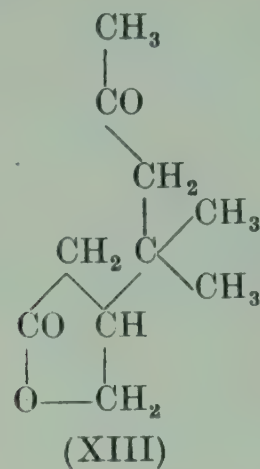
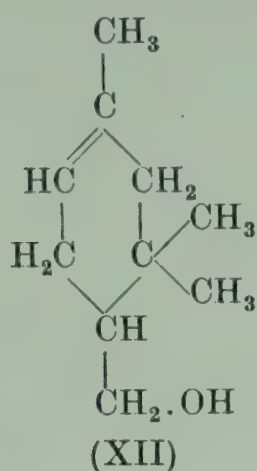
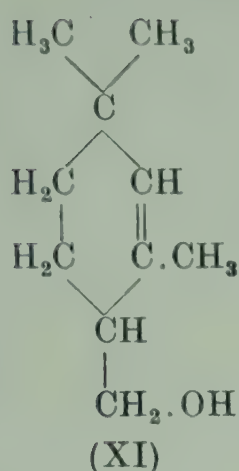
acetone, and only a trace of formaldehyde, thus confirming the isopropylidene structure. The properties of dihydrolavandulol are very similar to those of citronellol.

When lavandulol is heated with formic acid it undergoes cyclisation to give *cyclolavandulol*, b.p. 97–99°/11 mm., $\alpha_D + 24.7^\circ$ (*allophanate*, m.p. 157–158°; *dl*-, m.p. 160°); *dl-dihydro-cyclolavandulol*, b.p. 98–100°/12 mm. (*allophanate*, m.p. 163–164°) is obtained by hydrogenation of the *dl-cyclo*-alcohol.[†] If the cyclisation occurred in a similar way to that of geraniol to *cyclogeraniol*, the product would be expected to have the structure (XI); on oxidation with permanganate, however, it gives a compound C₁₀H₁₆O₃ (*semicarbazone*, m.p. 212–213°), possibly a keto-lactone, and the formula (XII) for *cyclolavandulol* is therefore more probable, the keto-lactone then being formulated as (XIII).[‡]

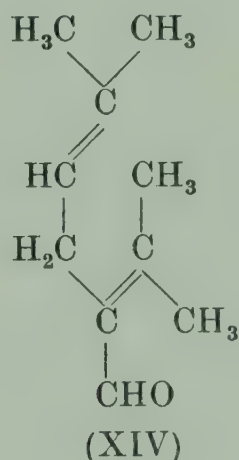
* *Helv. Chim. Acta*, 1946, **29**, 1133.

† Bourquin, Simon, Schäppi, Steiner and Schinz, *ibid.* 1949, **32**, 1564.

‡ Simon and Schinz, *ibid.* p. 1568.



By the oxidation of *dl*-lavandulol by a modified Oppenauer method, Lauchenauer and Schinz* have obtained *isolavandulal* (XIV) (2:4-dinitrophenylhydrazone, m.p. 155°) in which one of the double bonds has moved into conjugation with the aldehyde group.



LINALOOL

(Vol. I, p. 57)

An improved method for the oxidation of linalool to citral, using the dichromate-sulphuric acid process, has been described by Stoll and Commarmont.†

CITRONELLAL

(Vol. I, p. 71)

Naves and Ardizio‡ have recorded the absorption spectrum of citronellal in alcohol; the results differ appreciably from those previously reported.

* *Helv. Chim. Acta*, 1949, **32**, 1265.

‡ *Ibid.* 1948, **31**, 1240.

† *Ibid.* 1949, **32**, 1354.

Further investigations on the formation of hydroxydihydro-citronellal from the bisulphite compound of citronellal have been made by Stoll and Bolle* (compare Vol. I, p. 78).

Dihydrocitronellal (2:4-dinitrophenylhydrazone, m.p. 93°) has been obtained by a modified Oppenauer oxidation of dihydro-citronellol† (compare Vol. I, p. 79).

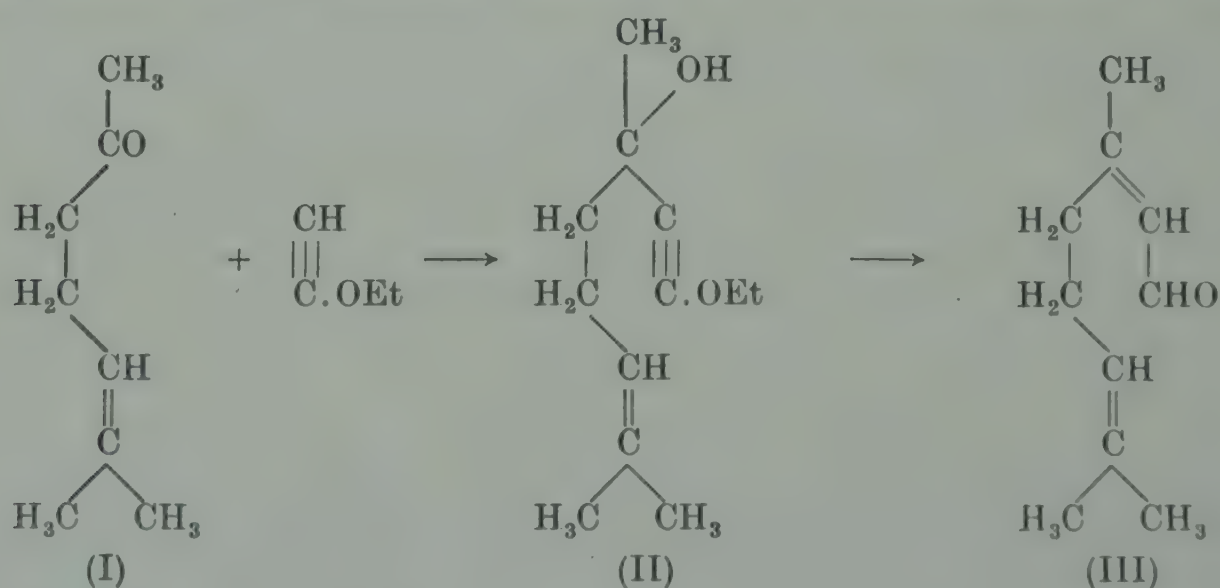
The kinetics of the acid-catalysed cyclisation of citronellal have been studied by Price and Dickman.‡

CITRAL

(Vol. I, p. 83)

The absorption spectrum of citral in alcohol, determined by Naves and Ardizio§ differs from the results of earlier investigators.

Arens and van Dorp|| have described a synthesis of citral, in which 2-methylhept-2-en-6-one (I) (obtained from isoprene hydrobromide and ethyl acetoacetate) was condensed with ethoxyacetylenemagnesium bromide to give 1-ethoxy-3-hydroxy-3:7-dimethyloct-6-en-1-yne (II); semihydrogenation and treatment with dilute hydrochloric acid (an anionotropic rearrangement occurs at this stage) gave citral (III). In view of the fact that the use of isoprene hydrobromide for the synthesis of lavandulol gave almost exclusively the isopropylidene form



* *Helv. Chim. Acta*, 1948, **31**, 1.

† Lauchenauer and Schinz, *ibid.* 1949, **32**, 1265.

‡ *Ind. Eng. Chem.* 1948, **40**, 257.

§ *Helv. Chim. Acta*, 1948, **31**, 1240.

|| *Rec. trav. chim.* 1948, **67**, 973.

(see p. 484), it would be of interest to examine the synthetic citral in order to determine whether it contains any appreciable amount of the *isopropenyl* form, which is usually encountered in varying amounts in the natural aldehyde.

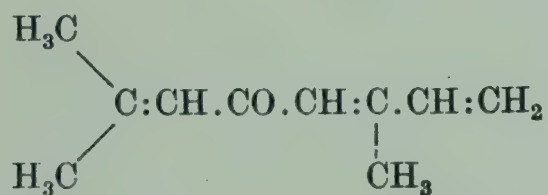
There have been considerable discrepancies in the recorded melting-points of the 2:4-*dinitrophenylhydrazone* of citral, which range from 96° to 134°. The derivative is clearly unsuitable for identification, and probably exists in polymorphic modifications.*

Price and Dickman[†] have studied the acid-catalysed cyclisation of citral (compare Vol. I, p. 91).

The preparation of *citrylideneacetic acid*, b.p. 138–142°/0.4 mm., n_D^{25} 1.5211, by Reformatsky condensation between citral and ethyl bromoacetate, has been described by Royals.[‡]

TAGETENONES

From the oil of *Lippia asperifolia* Rich., Naves[§] isolated a mixture of ketones, $C_{10}H_{14}O$, b.p. 63–64°/2 mm., d_4^{20} 0.9033, n_D^{20} 1.5003, $\alpha_D \pm 0^\circ$. Hydrogenation of this fraction over platinum gave 2:6-dimethyloctan-4-one, identical with tetrahydrotagetone (Vol. I, p. 103) (*semicarbazone*, m.p. 92°; *phenylsemicarbazone*, m.p. 96°). The ketones have provisionally been named tagetenones, and, since a high yield of ketone is obtained when they are treated with boiling 70 per cent sulphuric acid, a structure of the following type (with probable double-bond isomerides) is likely:



* Compare Naves and Ardizio, *Helv. Chim. Acta*, 1948, **31**, 1926.

† *Ind. Eng. Chem.* 1948, **40**, 257.

‡ *J. Amer. C.S.* 1947, **69**, 841.

§ *Helv. Chim. Acta*, 1948, **31**, 29.

CYCLOGERANIOLS

(Vol. I, p. 114)

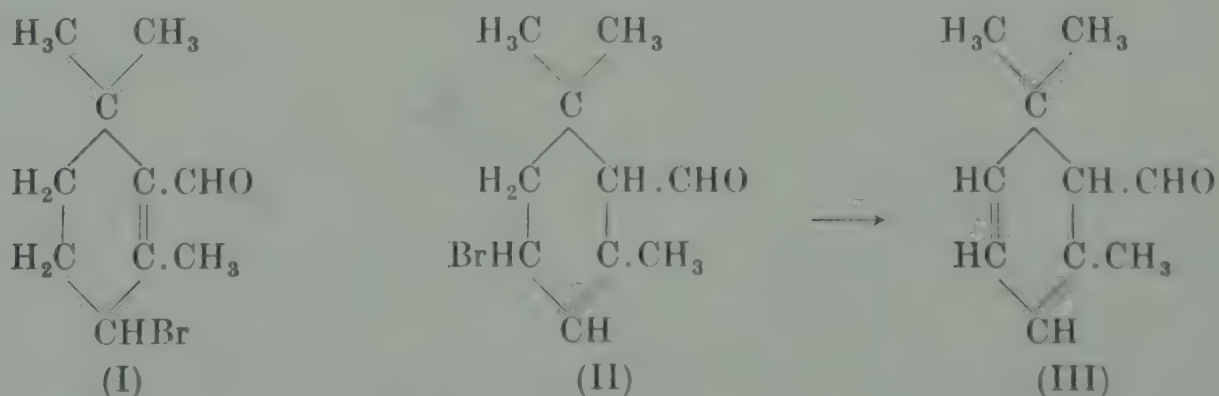
Lauchenauer and Schinz* have described a modified Oppenauer method of oxidation, which can be used for the conversion of α - and β -cyclogeraniols, and of dihydrocyclogeraniol, to the corresponding *cyclocitrals* and dihydrocyclocitral, respectively.

CYCLOCITRALS

(Vol. I, p. 116)

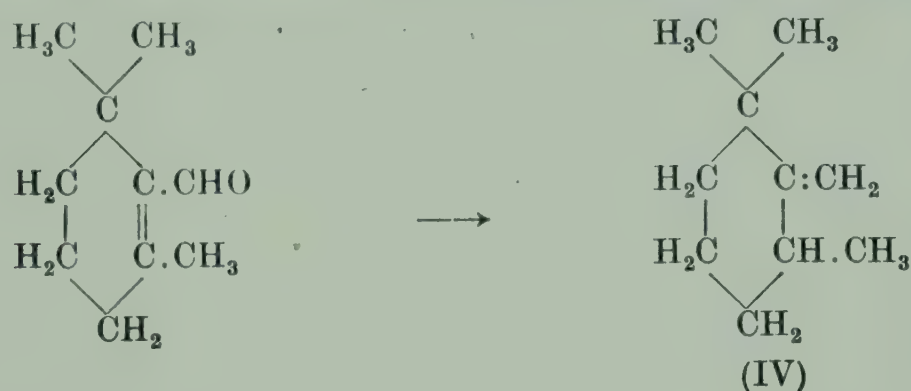
According to Young and Linden† the regeneration of β -cyclocitral from its semicarbazone is preferably done with cold dilute sulphuric acid, in order to avoid rearrangement to the α -form. The product thus obtained had b.p. 92–96°/12 mm., n_D^{21} 1.4971, n_D^{25} 1.4957, λ max. 2490 Å. (ϵ 11,600), and on ozonisation gave pure geronic acid, with no isogeronic acid.

Karrer and Ochsner‡ have investigated the reaction of β -cyclocitral with *N*-bromosuccinimide, in the hope of obtaining the bromo-derivative (I), which on dehydrobromination would be expected to yield safranal (Vol. I, p. 120). A mixture was obtained, however, which on treatment with collidine gave a product from which a small yield of a *semicarbazone*, m.p. 215°, was isolated. This was not a derivative of safranal, but probably of the isomeric compound, 2:2:6-trimethylcyclohexa-3:5-diene-1-aldehyde (III); the same product was obtained from α -cyclocitral, and the bromide mixtures presumably contain (II), a shift of the double bond evidently occurring during the reaction with β -cyclocitral.

* *Helv. Chim. Acta*, 1949, 32, 1265.‡ *Helv. Chim. Acta*, 1949, 32, 2092.† *J. Amer. C.S.* 1947, 69, 2072.

Rearrangement also occurs, though in a different direction, when β -cyclocitral is reduced by the Kishner-Wolff method, using hydrazine and sodium ethoxide.* The hydrocarbon obtained is 1:1:3-trimethyl-2-methylenecyclohexane (IV).

A new dihydrocyclocitral (semicarbazone, m.p. 206°), a stereoisomer of that previously described (semicarbazone, m.p. 185°) (see Vol. I, p. 119), has been obtained by hydrogenation of β -cyclocitral over a palladium-barium carbonate catalyst.†



The 2:4-dinitrophenylhydrazones of the α - and β -cyclocitral have m.p.s 157° and 172 – 173° respectively‡ (compare Vol. I, p. 119, where the value given is erroneous).

THE IONONES

(Vol. I, p. 122)

It has been shown that the essential oil of *Boronia megastigma* Nees contains not only β -, but also *d*- α - and *dl*- α -ionone,[§] and that oil of costus contains α - and β -ionones and *cis*-dihydroionone.^{||}

Naves[¶] has obtained what are probably the pure *d*- and *l*-forms of α -ionone by a repetition of the earlier resolution with *l*-menthylhydrazine (compare Vol. I, p. 127). The physical constants are: b.p. $87^\circ/2$ mm., $d_4^{20^\circ}$ 0.9288, $n_D^{20^\circ}$ 1.4971, $[\alpha]_D^{20^\circ}$ $+401^\circ$, -408° ; semicarbazone, m.p. 157° ; phenylsemicarbazone, m.p. 181° ; 2:4-dinitrophenylhydrazone, m.p. 133° ; *p*-bromophenylhydrazone, m.p. 172° .

* Lardelli and Jeger, *ibid.* p. 1817.

† Prelog and Frick, *ibid.* 1948, 31, 417.

‡ Lauchenauer and Schinz, *ibid.* 1949, 32, 1265.

§ Naves and Parry, *ibid.* 1947, 30, 419; compare Naves, *ibid.* p. 956.

|| Naves, *ibid.* 1949, 32, 1064. ¶ *Ibid.* 1947, 30, 769.

β -Ionone gives a *phenylsemicarbazone*, m.p. 162° ,* and a *2:4-dinitrophenylhydrazone*, m.p. 129° .†

Several more investigations of the absorption spectra of the ionones and their derivatives have recently been described.‡

Naves and Ardizio§ have shown that when hydrogenated in alcohol over Raney nickel β -ionone gives not only *dihydro- β -ionone* (I) (*semicarbazone*, m.p. 161 – 163° ; *phenylsemicarbazone*, m.p. 136°) but also *cis-dihydroionone* (II), b.p. $100^\circ/3$ mm., (*semicarbazone*, m.p. 185 – 186° ; *phenylsemicarbazone*, m.p. 176° ; *2:4-dinitrophenylhydrazone*, m.p. 177 – 178°). The latter is a stereoisomer of the *trans-dihydroionone*, m.p. 50° (*semicarbazone*, m.p. 110° ; *phenylsemicarbazone*, m.p. 195°), obtained by Prelog and Frick|| by condensation of a dihydrocyclocitral with acetone (compare p. 491). Hydrogenation of the solid dihydroionone gives *trans-tetrahydroionone* (III), b.p. $121^\circ/12$ mm., $d_4^{22^\circ}$ 0.9064 , $n_D^{22^\circ}$ 1.4634 (*semicarbazone*, m.p. 163° ; *phenylsemicarbazone*, m.p. 133°). The *cis*-form of (III) has $d_4^{22^\circ}$ 0.9138 , $n_D^{22^\circ}$ 1.4660 (*semicarbazone*, m.p. 183 – 184° ; *phenylsemicarbazone*, m.p. 109 – 110°). By reduction of the two tetrahydro-compounds with hydrazine and sodium ethoxide, the two forms of *tetrahydroionane* (IV) are obtained; *cis*-, $d_4^{20^\circ}$ 0.8280 , $n_D^{20^\circ}$ 1.4552 ; *trans*-, $d_4^{20^\circ}$ 0.8214 , $n_D^{20^\circ}$ 1.4531 .

Reduction of *l*- α -ionone (see above) gives *dihydro-l- α -ionone* (V) (*semicarbazone*, m.p. 153° , *2:4-dinitrophenylhydrazone*, m.p. 85°) and then *cis-tetrahydro-l-ionone* (III) (*semicarbazone*, m.p. 184° ; *2:4-dinitrophenylhydrazone*, m.p. 114°).

Of considerable interest is the isolation from ambergris of *dihydro- γ -ionone* (VI),¶ b.p. 116 – $118^\circ/10$ mm., $d_4^{22^\circ}$ 0.9347 , $n_D^{22^\circ}$ 1.4789 , $\alpha_D + 1.5^\circ$ (*semicarbazone*, m.p. 189 – 190°). The presence of the olefinic methylene group is shown by ozonolysis to yield formaldehyde and a diketone, which must be formulated as (VII). Hydrogenation of (VI) gives a tetrahydroionone, *semicarbazone*, m.p. 179 – 180° , *phenylsemicarbazone*, m.p. 108 – 109° , which is probably the *cis*-form of (III) described above. The

* Naves and Bachmann, *Helv. Chim. Acta*, 1949, **32**, 966.

† Naves and Ardizio, *ibid.* 1948, **31**, 1926.

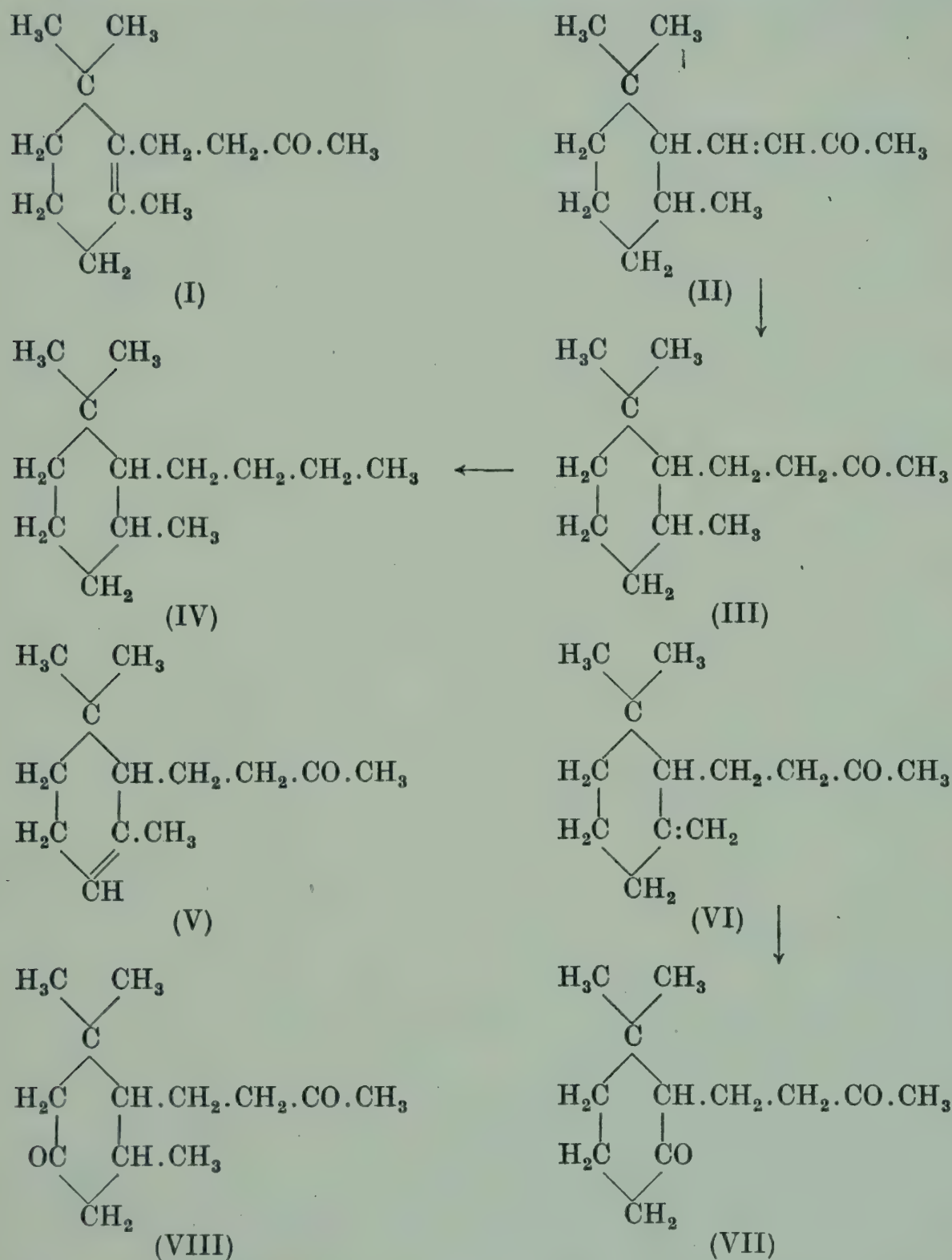
‡ Naves, *ibid.* p. 2057; Naves and Ardizio, *ibid.* pp. 1427, 1926; 1949, **32**, 1228; Lusskin and Winston, *J. Amer. C.S.* 1949, **71**, 2412; Jones and Braude, *ibid.* 1950, **72**, 1041.

§ *Helv. Chim. Acta*, 1949, **32**, 206.

|| *Ibid.* 1948, **31**, 417.

¶ Ruzicka, Seidel and Pfeiffer, *ibid.* p. 827.

partial conversion of dihydro- α -ionone into dihydro- γ -ionone has been recorded by Ruzicka, Büchi and Jeger,* who found that the product prepared by the addition of hydrogen chloride to (V), gave on dehydrochlorination a mixture of (V) and (VI).



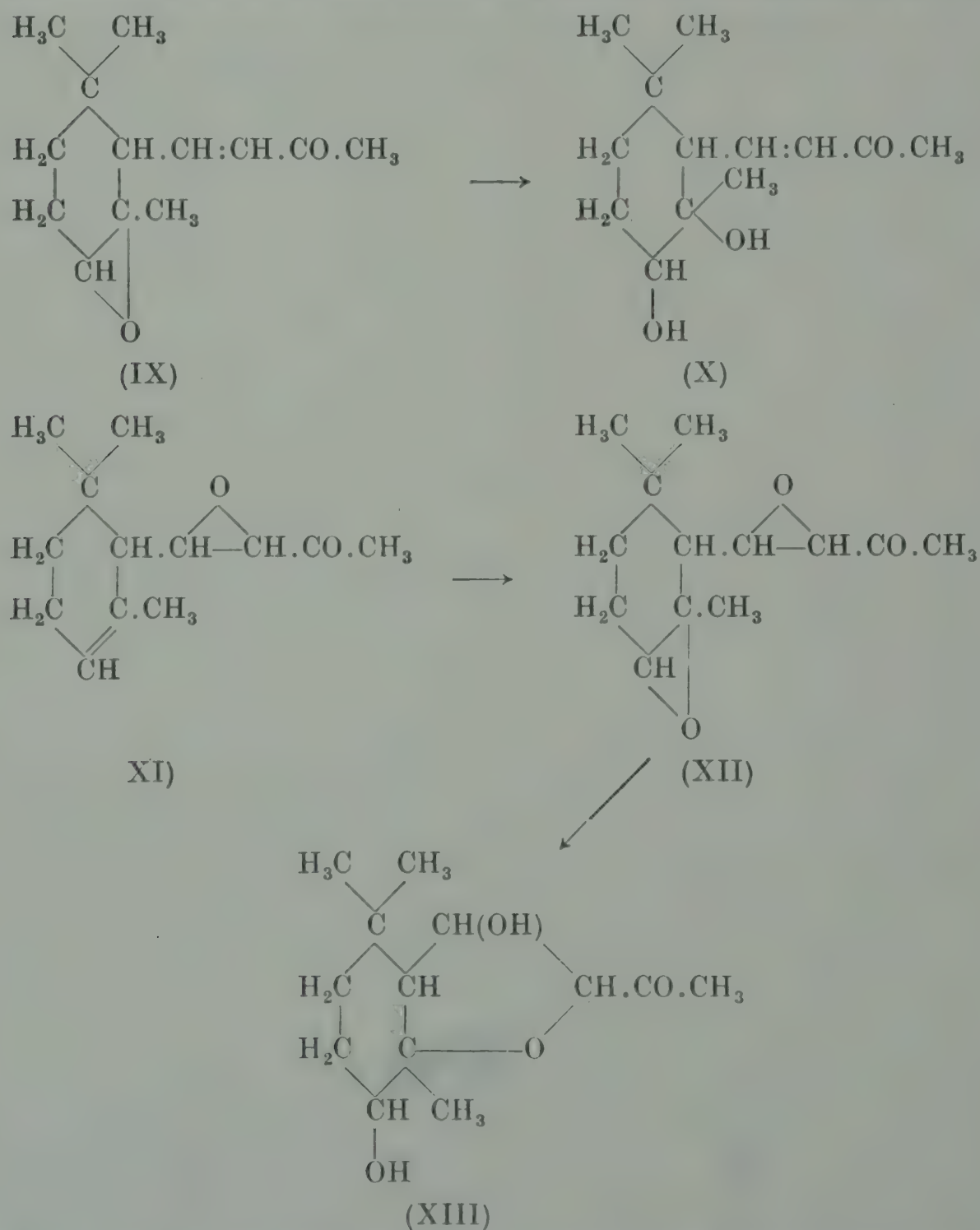
5-Keto-cis-tetrahydroionone (VIII) has been shown to occur in the urine of pregnant mares, and also in the scent glands of the Canadian beaver.[†]

* *Ibid.* p. 293.

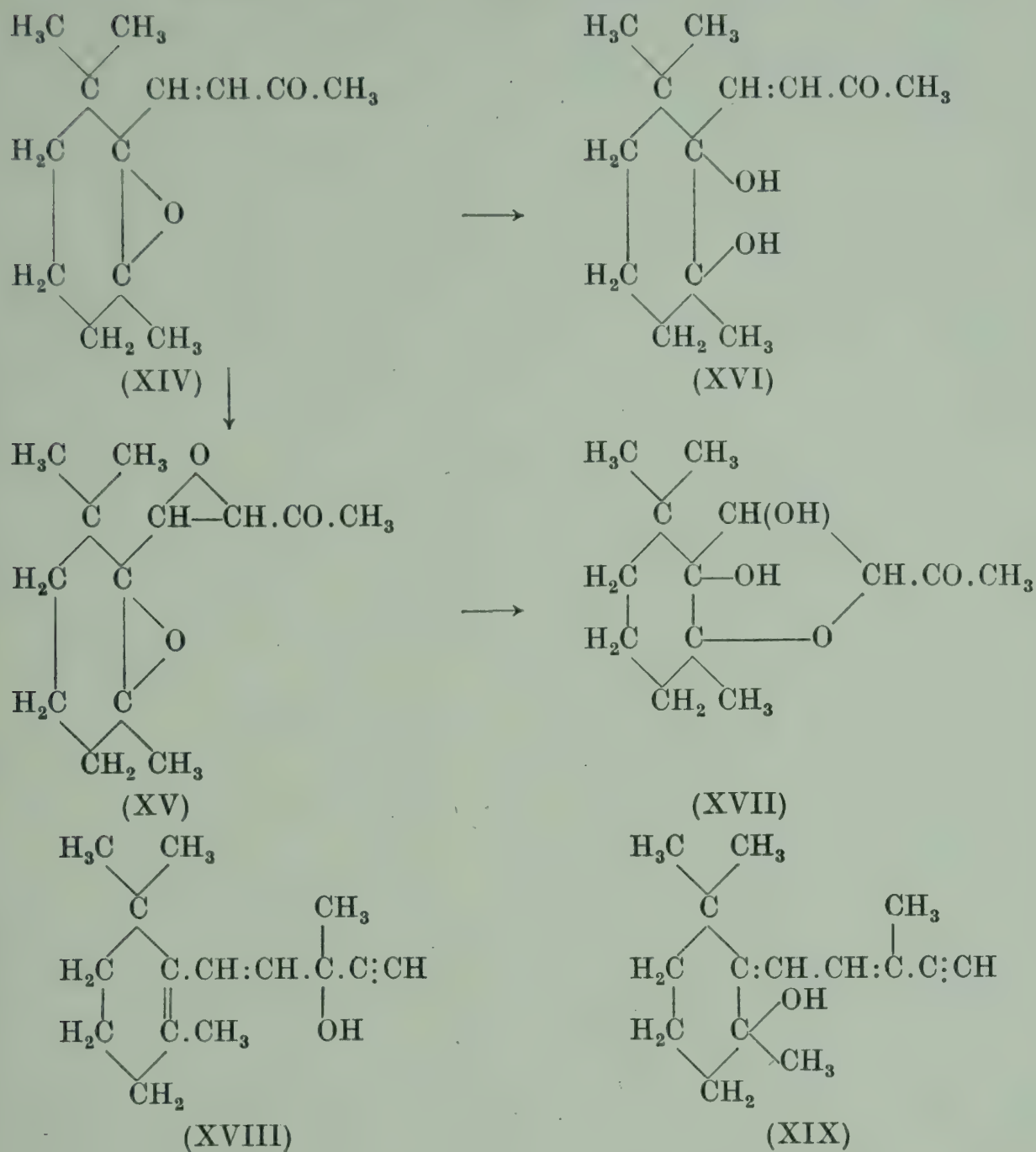
[†] Prelog, Führer, Hagenbach and Schneider, *ibid.* p. 1799; Prelog and Frick, *ibid.* p. 2135; Lederer, Prelog and Schneider, *ibid.* p. 2133.

Karrer and Stürzinger* have described several epoxides of the ionones. When α -ionone is treated with perphthalic acid it gives the 3:4-epoxide (IX), b.p. 146–148°/13 mm., hydrolysis of which gives the glycol (X), m.p. 128°. With hydrogen peroxide in alkaline solution, however, α -ionone gives the 2':3'-epoxide (XI), m.p. 38°, which on subsequent treatment with perphthalic acid gives the 3:4-2':3'-diepoxide (XII), b.p. 90–100°/0.05 mm.; hydrolysis of the latter yields 2-acetyl-3:8-dihydroxy-5:5:9-trimethylhexahydrocoumarane (XIII), m.p. 141°.

β -Ionone gives no recognisable product with alkaline peroxide,



* *Helv. Chim. Acta*, 1946, **29**, 1829; compare Naves, Schwarzkopf and Lewis, *ibid.* 1947, **30**, 880.



but with perphthalic acid it gives the 2:3-epoxide (XIV), m.p. 46° , which then reacts normally with alkaline peroxide and yields the 2:3-2':3'-diepoxide (XV), m.p. 75° . On hydrolysis, the monoepoxide gives the corresponding glycol (XVI), m.p. 111° , whilst the diepoxide gives a product which is probably 2-acetyl-3:4-dihydroxy-5:5:9-trimethylhexahydrocoumarane (XVII), m.p. 150° .

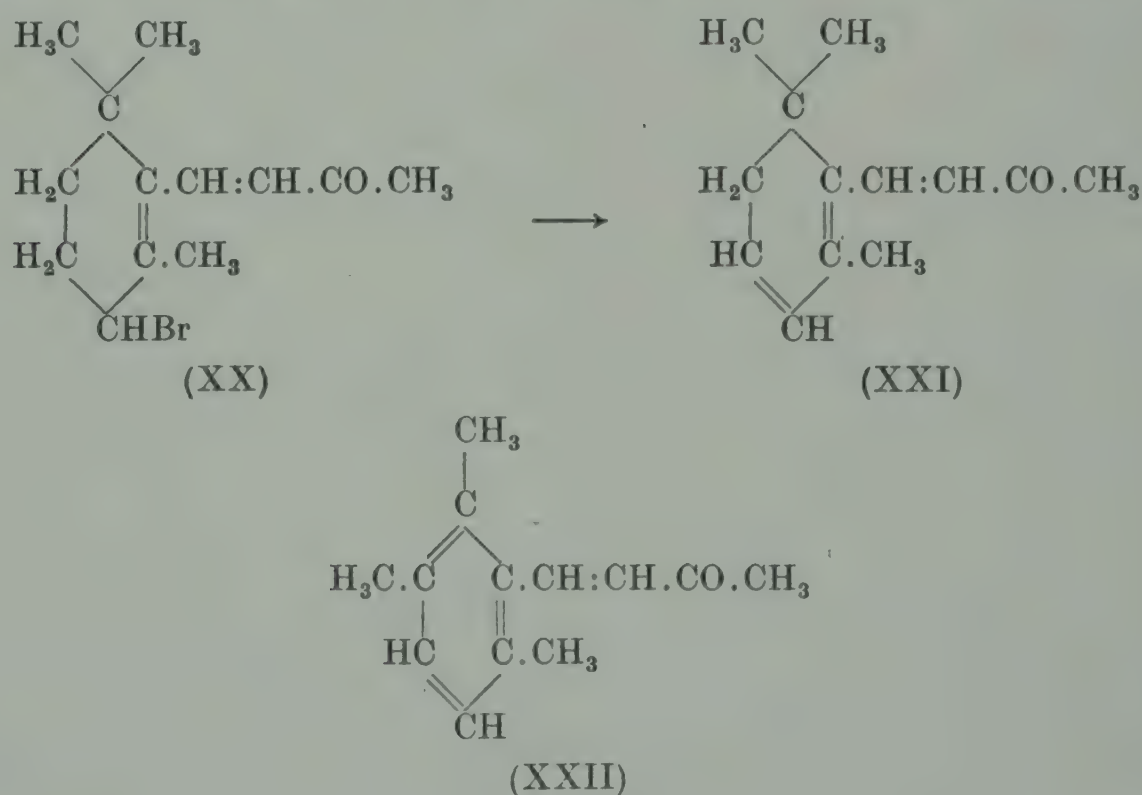
Karrer and Benz* consider that when β -ionone reacts with sodium acetylide the product is not the normal acetylenic alcohol (XVIII) but the anionotropically rearranged alcohol (XIX). As Oroshnik and Mebane† point out, however, the light absorption maximum at 3060 Å. is anomalous for such a

* *Ibid.* 1948, 31, 390.

† *J. Amer. C.S.* 1949, 71, 2062.

structure, and corresponds more closely to that expected for a dehydration product. The latter authors have found that the normal product (XVIII) can be obtained if lithium or calcium acetylide is used.*

By the action of *N*-bromosuccinimide on β -ionone, an unstable bromo-compound, probably (XX), is formed, which on dehydrobromination under mild conditions with diethylamine, dimethylaniline, or silver oxide, gives *dehydro- β -ionone* (XXI), b.p. $75^\circ/1\text{ mm.}$, n_D^{22} 1.5497 (*semicarbazone*, m.p. $144\text{--}146^\circ$; *phenylsemicarbazone*, m.p. 148° , *2:4-dinitrophenylhydrazone*, m.p. $150\text{--}151^\circ$);[†] dehydrobromination under more vigorous conditions results in aromatisation of the ring. With α -ionone, a normal dehydro-compound could not be obtained;[‡] dehydrobromination with silver oxide gave *2:3:6-trimethylbenzalacetone* (XXII).



IRONE

(Vol. I, p. 130)

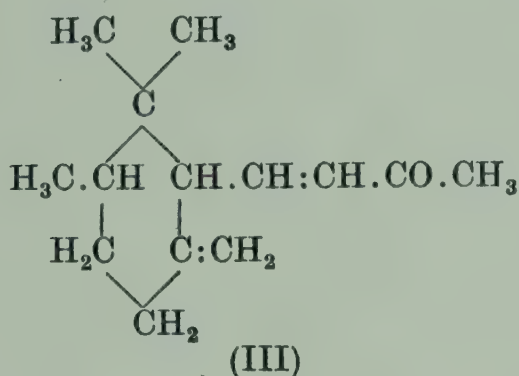
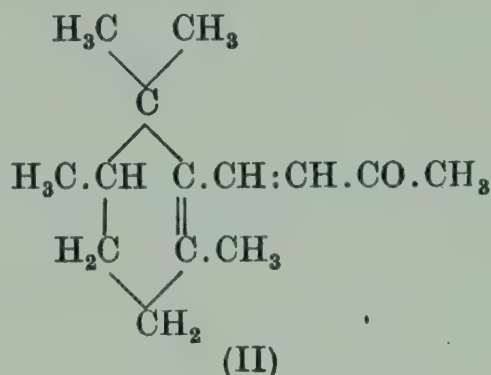
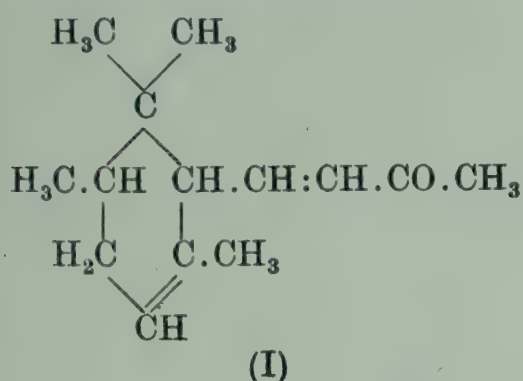
The far-reaching discoveries which have been made in recent years on the chemistry of irone have necessitated a revision of several previously accepted conclusions. It is now recognised

* See also U.S.P. 2425201.

[†] Henbest, *Nature*, 1948, 161, 481; Büchi, Seitz and Jeger, *Helv. Chim. Acta*, 1949, 32, 39.

[‡] Karrer and Ochsner, *ibid.* 1948, 31, 2093.

that irone is 6-methylionone, and that it can exist in the α -, β -, and γ -forms (I), (II) and (III), each of which has several stereoisomeric modifications.*



The first indication that the structure previously assigned to irone required revision appeared in 1947, when Naves, Grampoloff and Bachmann[†] described the synthesis of a 6-methylionone from 2:3-dimethylhept-2-en-6-one (IV), the synthesis of which had been achieved by Kilby and Kipping[‡] and by Ruzicka and Schinz.[§] Naves and his collaborators found that by the condensation of (IV) with acetylene the acetylenic alcohol (V) could be prepared, which on semihydrogenation gives 3-methyl-linalool (VI), b.p. 94–95°/10 mm., d_4^{20} 0.8737, n_D^{20} 1.4671. By the oxidation of this alcohol with chromic acid 3-methylcitral (VII), b.p. 116–117°/10 mm., d_4^{20} 0.8990, n_D^{20} 1.4935 (*semicarbazones*, m.p.s 183–184° and 209°) was obtained, which on condensation with acetone yielded 3-methylpseudoionone (VIII), b.p. 127–128°/3 mm., d_4^{20} 0.9014, n_D^{20} 1.5345 (*semicarbazones*, m.p.s 177° and 190°; *phenylsemicarbazones*, m.p.s 171° and 182°). The 3-methylpseudoionone was also prepared by rearrangement of the 3-methyl-linalool, by acetylation and saponification, into 3-methylgeraniol (IX), b.p. 119–120°/10 mm., d_4^{20} 0.8919, n_D^{20}

* Stereoisomers are distinguished by the use of the prefixes *iso*-, *neo*-, etc. (see p. 504).

† *Helv. Chim. Acta*, 1947, **30**, 1599.

‡ *J.C.S.* 1939, p. 435.

§ *Helv. Chim. Acta*, 1940, **23**, 959.

m.p. 120°). The close similarity between the constants of irone and the synthetic 6-methylionone, and also between those of the natural and synthetic tetrahydro-derivatives, provided strong evidence for the assignment to irone of a 6-methylionone structure; furthermore, this formula accounts more readily for the formation of irene (X) than did that previously considered to represent irone.

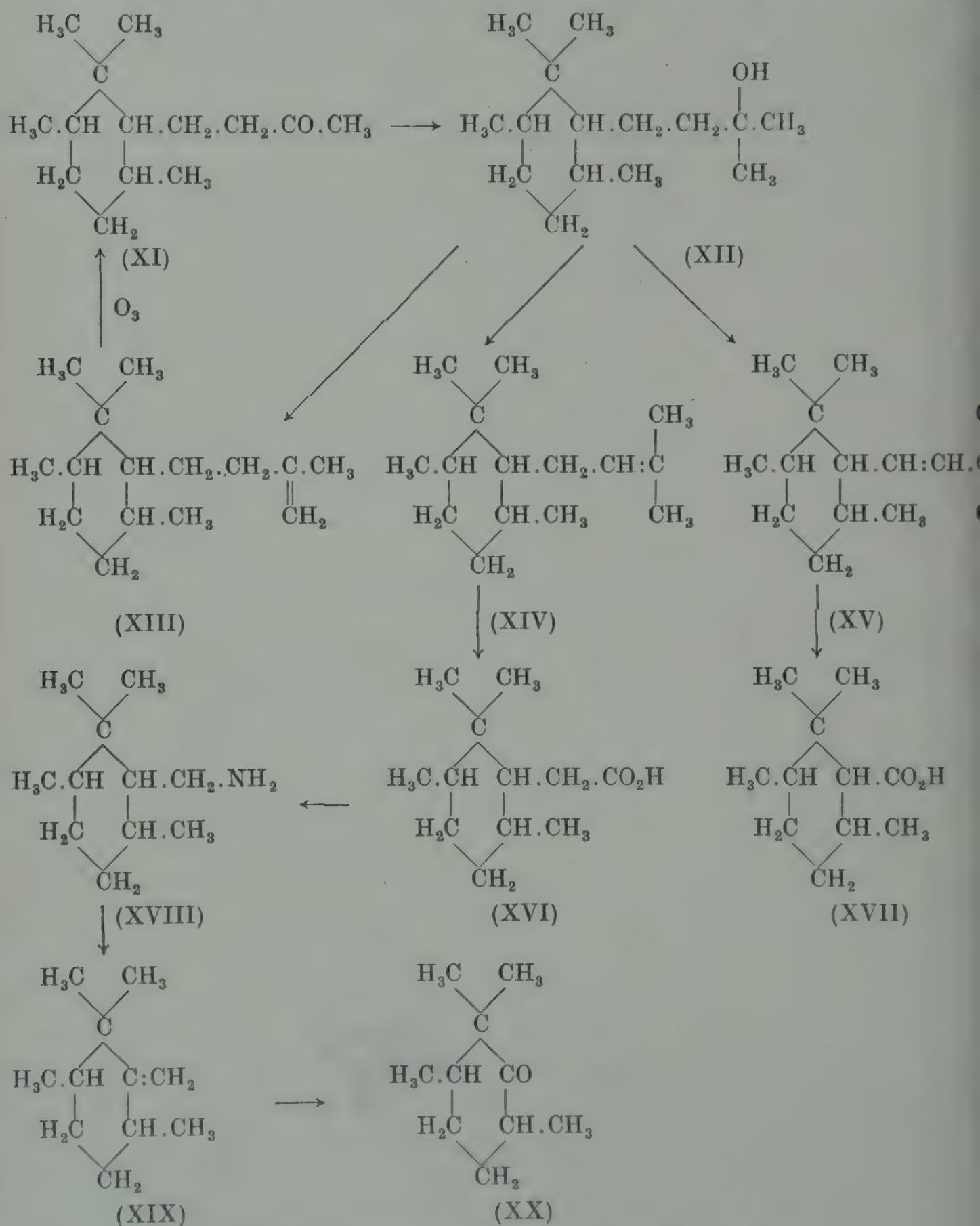
Similar conclusions were published very shortly afterwards by Ruzicka and his co-workers,* who had independently synthesised a 6-methylionone by a route essentially identical with that used by Naves, *via* 3-methylgeraniol, except that the final cyclisation was carried out with phosphoric acid. Their product had b.p. $68-73^{\circ}/0.008$ mm., $d_4^{19^{\circ}}$ 0.9345, $n_D^{19^{\circ}}$ 1.5001, and gave a *phenylsemicarbazone*, m.p. $166-167^{\circ}$; it was probably a mixture of α - and *iso*- α -irone. They made the important observation that formaldehyde was formed when natural irone was subjected to ozonolysis, thus indicating the existence of γ -irone (III). Furthermore, whereas formaldehyde was obtained by ozonolysis of the ketone regenerated from the phenylsemicarbazone of m.p. 178° , none was obtained from the ketone derived from the phenylsemicarbazone of m.p. 155° ; the latter compound was therefore probably a derivative of α -irone.

Important confirmatory evidence of the structure of irone was afforded by degradation of *tetrahydroirone* (XI), b.p. $135-136^{\circ}/10$ mm., $d_4^{15^{\circ}}$ 0.925, $[\alpha]_D + 35^{\circ}$, obtained from natural irone.[†] Treatment of this ketone with methylmagnesium iodide gave the tertiary alcohol (XII) which on dehydration with formic acid gave a mixture of the three hydrocarbons (XIII), (XIV) and (XV). Ozonolysis of this mixture gave the two acids (XVI) and (XVII), from (XIV) and (XV) respectively, and tetrahydroirone from (XIII). The acid (XVI) was converted into the amine (XVIII) by the Curtius method, and degradation by the Hofmann exhaustive methylation process gave the hydrocarbon (XIX), ozonolysis of which gave 2:2:3:6-tetramethylcyclohexanone (XX) (*semicarbazone*, m.p. $214-215^{\circ}$), identical with a synthetic specimen. This conclusively proves the nature of the

* Ruzicka, Seidel, Schinz and Pfeiffer, *Helv. Chim. Acta*, 1947, **30**, 1807; Schinz, Ruzicka, Seidel and Tavel, *ibid.* p. 1810.

[†] Ruzicka, Seidel and Brugger, *ibid.* p. 2168; Schäppi and Seidel, *ibid.* p. 2199.

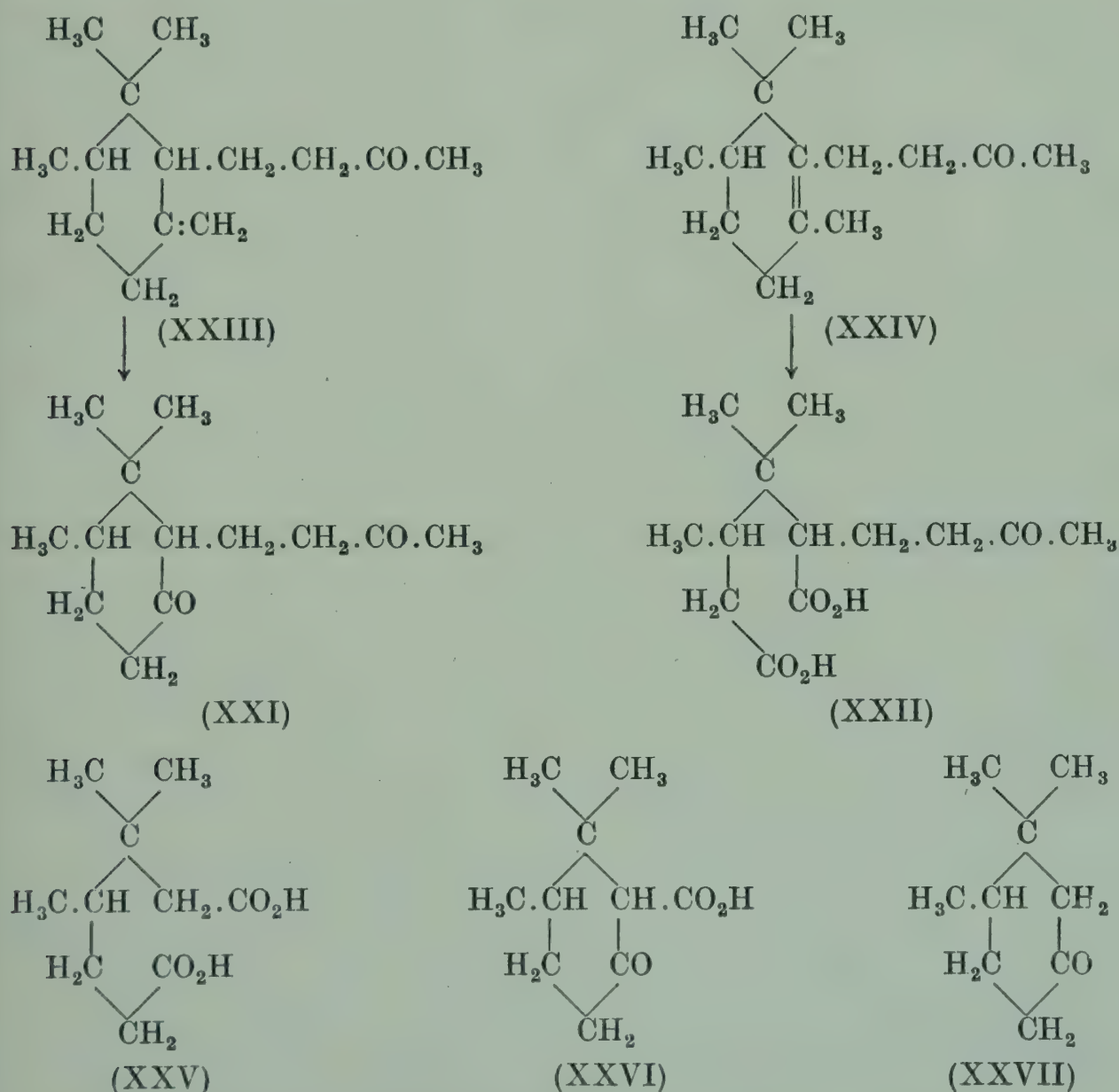
ring in irone. Further evidence was later provided by studies on the degradation of dihydroirone and dihydroirane.* Ozonolysis of dihydroirone from natural irone, followed by chromic acid oxidation, gave a diketone $C_{13}H_{22}O_2$ and a ketonic dicarboxylic acid $C_{13}H_{22}O_5$. The formation of these products, which must be



* Ruzicka and Seidel, *Helv. Chim. Acta*, 1948, 31, 160.

formulated as (XXI) and (XXII) respectively, can only be explained if both dihydro- γ -irone (XXIII) and dihydro- α -irone (XXIV) were present.

The earlier formulation of irone as a *cycloheptene* derivative (see Vol. I, p. 130) was based largely on the isolation of $\beta\beta\gamma$ -trimethylpimelic acid (XXV) from the ozonolysis products. The recognition of γ -irone as a constituent of natural irone has provided an explanation for the formation of (XXV), which is probably derived by "acidic" hydrolysis of the intermediate β -keto-acid (XXVI); 3:3:4-trimethylcyclohexanone (XXVII), derived by "ketonic" hydrolysis of (XXVI), has also been isolated.*



Although there is general agreement on the structures of the irones, unfortunately there are considerable differences in opinion

* Ruzicka, Seidel, Schinz and Tavel, *ibid.* p. 257.

between the schools of Naves and Ruzicka on the relative proportions present in the natural oil, on the reliability of physical and chemical methods of estimation, on the conditions of isomerisation, and on several questions of priority. Consequently, many publications have been of a polemical nature and have contained arguments into which it is not proposed to enter in the present account. Some, though not all, of the differences can probably be explained by variations in the natural materials used by the two groups of investigators.

The quantitative estimation of the amounts of α -, β -, and γ -irones present in a mixture of the three is, in theory, quite straightforward. β -Irene, containing a triply conjugated system, shows a characteristic light absorption maximum at 2950 A., the intensity of which can be used to determine the amount of this isomer. γ -Irene is the only one which yields formaldehyde on ozonolysis, so that its estimation by such means should be possible; α -irone would then be determined by difference. Ruzicka* finds that with his technique pure γ -irone and pimelic acid (which also contains an olefinic methylene group) give only 34–36 per cent of the theoretical amount of formaldehyde; in the estimation of γ -irone in natural irone, therefore, a correction is applied to allow for this, and on such a basis it is found that the γ -isomer is the main constituent, being present to the extent of about 70 per cent. Naves, on the other hand, maintains on the basis of physical evidence (particularly from Raman spectra) that in the majority of oils very little γ -irone is present, and that α -irone predominates.† Ruzicka considers that the Raman spectra are not capable of the accuracy claimed by Naves, and believes that infra-red spectra are more reliable;‡ results from the latter are in good agreement with the results of ozonolysis.§ Naves, however, criticises the ozonolysis technique used by Ruzicka, and describes a procedure which, on a micro-scale, gives accurate results when tested on pimelic acid and on pure γ -irone;|| when applied to specimens of natural irone, the

* Ruzicka, Seidel, Schinz and Tavel, *Helv. Chim. Acta*, 1948, **31**, 257; Seidel, Schinz and Ruzicka, *ibid.* 1949, **32**, 1739.

† Naves and Bachmann, *ibid.* 1947, **30**, 2222, 2233, 2241; 1949, **32**, 394; Naves and Ardizio, *ibid.* 1948, **31**, 1427; 1949, **32**, 1228; Naves, *ibid.* 1948, **31**, 2047; 1949, **32**, 1230.

‡ Günthard and Ruzicka, *ibid.* 1948, **31**, 642; 1949, **32**, 2125.

§ Günthard, Ruzicka, Schinz and Seidel, *ibid.* p. 2198.

|| Naves, *ibid.* 1948, **31**, 893; 1949, **32**, 1151, 2186.

majority gave only small proportions of formaldehyde, though in some the γ -irone content reached about 55 per cent. Ruzicka, remarking upon the much higher proportion of γ -irone now found by Naves, considers that the failure of the latter to obtain appreciable amounts of this isomer from other preparations may be due to the working conditions employed, since it is known that γ -irone can be isomerised to α - and β -irones.*

The conditions under which this isomerisation occurs have also led to polemical discussion. Although it is recognised that γ -irone is transformed into a mixture of α - and β -irones when treated with dilute sulphuric acid, formic acid, etc., and that the proportion of β -form increases as the conditions become more vigorous, Naves[†] considers that the isomerisation does not take place so readily as Ruzicka believes[‡] and that the initial product is *neo*- α -irone, which only with difficulty is isomerised to α - and then to β -irone. Isomerisation can also be accomplished under alkaline conditions, the end product again being mainly β -irone.[§] If, however, pure β -irone is treated with sodium ethoxide, some α -irone is formed;^{||} the system is therefore tautomeric, the equilibrium being largely on the β -side.

The problem of isomerisation arises also in any discussion of the cyclisation stage in the synthesis of irone; it is not surprising, therefore, that the nature of the product depends upon the conditions used. According to Naves[¶] cyclisation with either 62.5 per cent sulphuric acid or 85 per cent phosphoric acid at 50° gives a mixture rich in α -irone (probably mainly the *iso*-form); with concentrated sulphuric acid, however, Ruzicka obtains almost pure β -irone.** With boron trifluoride, α -irone is obtained, probably containing a smaller proportion of the *iso*-form. To Naves, who considers that α -irone is the main constituent of the natural ketone, the results with this catalyst are of particular significance. Ruzicka, although agreeing that some α -irone is formed, considers that not only the catalyst, but also the stereochemical composition of the *pseudo*-irone, is of importance.

* Ruzicka, Seidel, Schinz and Tavel, *ibid.* 1948, **31**, 257; Schinz, Seidel and Ruzicka, *ibid.* 1949, **32**, 2102, 2560; Naves, *ibid.* 1948, **31**, 893.

† *Ibid.* 1949, **32**, 1058.

‡ Ruzicka, Seidel, Schinz and Tavel, *ibid.* 1948, **31**, 257.

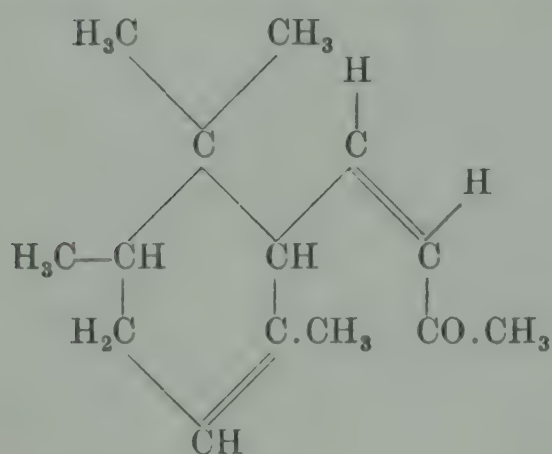
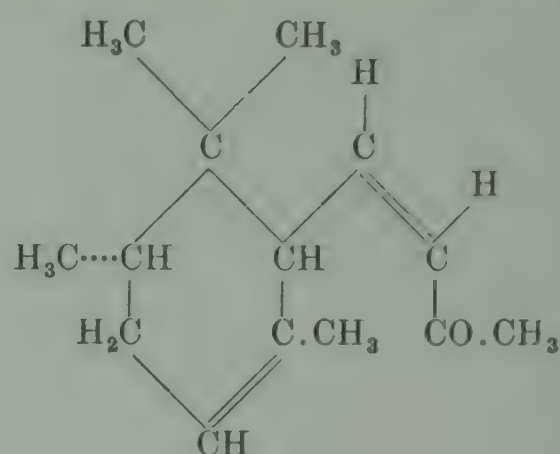
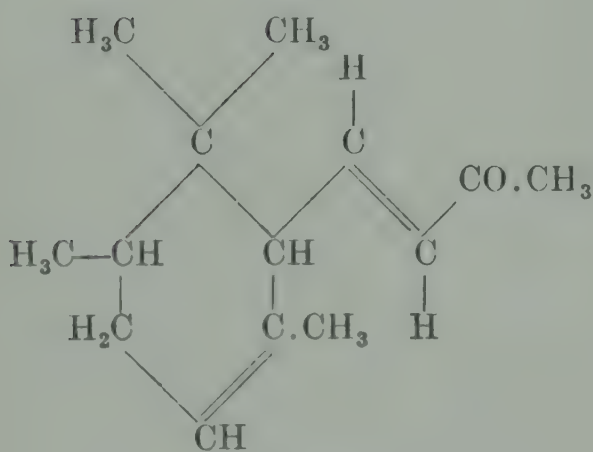
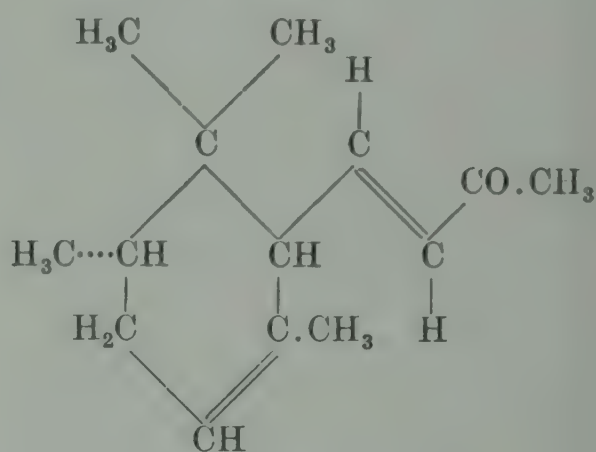
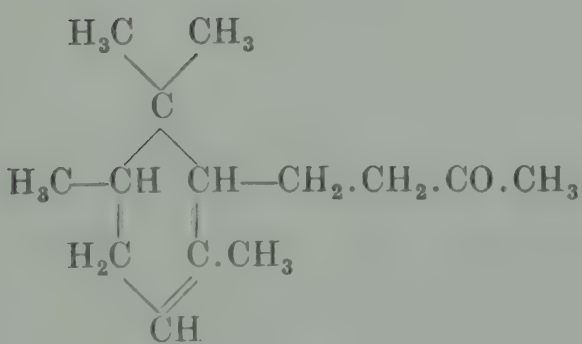
§ See also Köster, *Ber.* 1944, **77**, 559.

|| Naves, *Helv. Chim. Acta*, 1948, **31**, 1103.

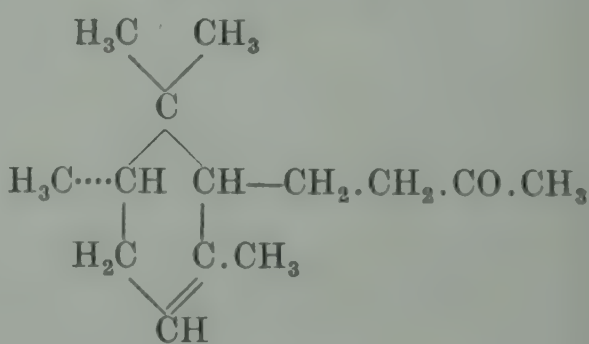
¶ *Ibid.* pp. 893, 1103.

** Seidel, Schinz and Ruzicka, *ibid.* 1949, **32**, 2102.

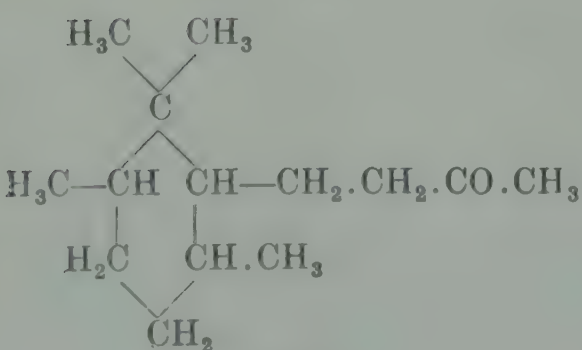
Apart from optically active forms, the α - and γ -irones can each exist in four stereoisomeric modifications, arising from the possibility of *cis-trans* isomerism both in the ring (position of the side chain at C_2 relative to the methyl group at C_6) and at the double bond in the side chain. β -Irone cannot exhibit the ring

 α -Ironeiso- α -Ironeneo- α -Ironeneoiso- α -Irone

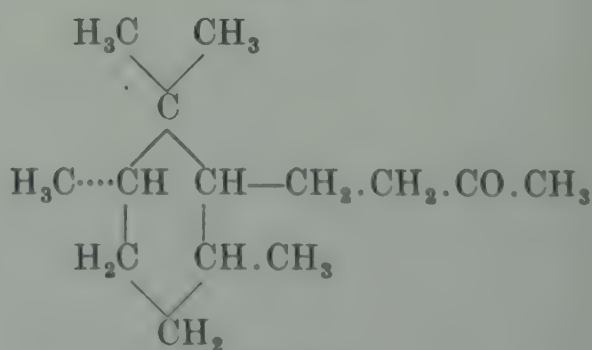
(XXVIII)



(XXIX)



(XXX)



(XXXI)

isomerism, since the cyclic double bond engages C_2 , and it therefore exists in two forms. Optical activity is possible in all cases. Naves* has suggested that irones with a *trans* relationship between C_2 and C_6 should be given the prefix "*iso*", and that those with a *trans* configuration about the side-chain double bond should carry the prefix "*neo*". The four forms of α -irone are illustrated on p. 504.

The separation of pure specimens of the stereoisomers is a difficult task, and is at present not complete. The methods used have consisted largely of fractional crystallisation of derivatives (particularly the phenylsemicarbazones). α -Irone was obtained by fractional distillation of irone regenerated from a phenylsemicarbazone of m.p. 154–159°, prepared from natural irone; *iso*- α -irone from a phenylsemicarbazone m.p. 174.5–175.5°, prepared from synthetic irone and from natural irone isomerised with alcoholic alkali; and *neo*- α -irone from a phenylsemicarbazone, m.p. 181.5–182°, obtained from natural irone† and also from the products of isomerisation of γ -irone. Some separation of *neo*- α -irone has also been achieved by differential reactivity with sodium bisulphite.‡ *neois*- α -Irone has not yet been described. Only one β -irone is known; it is conveniently prepared by isomerisation of α - or γ -irone with concentrated sulphuric acid or with alkali.§ Likewise, only one of the four possible γ -irones (*neo*- γ -irone) has been obtained.|| The physical constants of the known stereoisomers and of some hydrogenation products are given in the table; with very few exceptions, both groups of investigators have recorded similar figures.

The allocations of structures to these stereoisomers are based largely on physical evidence, and must be regarded as tentative, though several interrelationships have been established chemically. Thus, by hydrogenation of α - and *iso*- α -irones over Raney nickel under mild conditions only the double bond in the side chain is reduced, and two different dihydroirones are

* *Helv. Chim. Acta*, 1949, **32**, 969.

† Naves, *ibid.* 1948, **31**, 1876.

‡ Naves, *ibid.* p. 1280.

§ Köster, *Ber.* 1944, **77**, 553, 559; Naves, *Helv. Chim. Acta*, 1948, **31**, 893; Ruzicka, Seidel, Schinz and Tavel, *ibid.* p. 257; Seidel, Schinz and Ruzicka, *ibid.* 1949, **32**, 2102.

|| Naves, *ibid.* 1948, **31**, 893, 2047; Bächli, Seidel, Schinz and Ruzicka, *ibid.* 1949, **32**, 1744.

The Irones and their Derivatives

	B.p.	d_4^{20}	n_D^{20}	$[\alpha]_D$	M.p. of				
					Semicarbazone	Phenyl- semicarbazone	Thiosemi- carbazone*	2:4-Dinitro- phenyl- hydrazine	<i>p</i> -Bromo- phenyl- hydrazine†
α -Irone	109°/3 mm.	0.9340	1.4998	+226	103-104°	<i>d</i> 158° <i>dl</i> 165°	183°	126°	169-170°
<i>iso</i> - α -Irone	108°/3 mm.	0.9346	1.5013	-79.5°	157-158°	174-175° (<i>N</i>) 164-165° (<i>R</i>)	—	103°	—
<i>neo</i> - α -Irone	106°/2 mm.	0.9349	1.5009	-8.8°	164-165°	182°	189°	154°	164-165°
β -Irone	108°/2 mm.	0.9456	1.5180	+20° (<i>N</i>) +11° (<i>R</i>)	169°	169°	168°	135-136°	—
<i>neo</i> - γ -Irone	103°/1 mm.	0.9355	1.5019	+8°	114-115°	178-179°	170° (<i>N</i>) 128° (<i>R</i>)	146° (<i>N</i>) 130-131° (<i>R</i>)	178-179°
Dihydro- α -irone	107°/2 mm.	0.9303	1.4828	—	173°	—	—	130-131°	—
Dihydro- <i>iso</i> - α -irone	105°/2 mm.	0.9259	1.4806	—	144°	—	—	116-117°	—
Dihydro- β -irone	—	—	—	—	157-158° (<i>N</i>) 161-162° (<i>R</i>)	—	—	104-105°	—
Dihydro- γ -irone	104°/2 mm.	0.9376	1.4855	—	200°	—	—	109-110°	—
Tetrahydroirone	104°/2 mm.	0.9223	1.4742	—	201-202°	108-109° (?)	—	130°	—
Tetrahydroisoirone	102°/2 mm.	0.9143	1.4715	—	161-162°	—	—	115-116° (remelt 134-136°)	—

* Naves and Bachmann, *Helv. Chim. Acta*, 1949, 32, 599.

† *Idem*, *ibid.* p. 618.

(*N*) According to Naves.

(*R*) According to Ruzicka.

obtained.* Dihydro- α -irone is given the *cis* structure (XXVIII) on the basis of the Auwers-Skita rule, since it has a higher density and refractive index than dihydro-*iso*- α -irone (XXIX). Further hydrogenation leads to the tetrahydroirols, from which, by oxidation with chromic acid the two forms (XXX) and (XXXI) of the four possible tetrahydroirones are obtained. Of these, (XXX) is identical with the tetrahydroirone derived by a similar series of reactions from the known forms of β - and γ -irones, which must therefore have the same ring configuration (i.e. *cis*) as α -irone.[†] *neo*- α -Irone on mild hydrogenation gives dihydro- α -irone (XXVIII); consequently it also has the *cis* ring configuration.[‡] The configurations around the double bond in the side chain are based on considerations of Raman spectra, dielectric constants, etc., and on comparatively small differences in reactivity; for example, *neo*- α -irone is converted into irone less readily than α -irone, but forms an oxime more rapidly;[§] both of these observations are in harmony with a *trans*-structure about the side-chain double bond in the case of *neo*- α -irone.

During the many investigations on irone, some of the work which was carried out, although only providing negative or indirect evidence, was nevertheless of interest, and will now be briefly considered. Structural isomers of irone were prepared by Stoll and his co-workers,^{||} who obtained 4- and 5-methylionones by methods essentially similar to those used for the synthesis of irone; neither possessed the odour of irone. Naves and Ardizio[¶] applied the Diels-Alder reaction to 1:1:2-trimethylbutadiene, which condensed with crotonaldehyde to give a mixture of the two possible products (XXXII) and (XXXIII); reaction with acetone then gave a mixture, (XXXIV) and (XXXV), of “*iso*-irones”.^{**} Ruzicka, Seidel, Schinz and Pfeiffer^{††} studied the preparation of seven-membered-ring analogues of irone, and succeeded in synthesising 1:1:7-trimethyl-3-(*but*-1-en-3-onyl)cyclohept-2-ene (XXXVI), b.p. 160–162°/11 mm., $d_4^{23^\circ}$ 0.9581, $n_D^{32^\circ}$ 1.5391 (*semicarbazone*, m.p. 191–192°).

* Naves, *Helv. Chim. Acta*, 1948, **31**, 893, 1103, 1280, 1871.

† Naves, *ibid.* 1948, **31**, 2047; Bächli, Seidel, Schinz and Ruzicka, *loc. cit.*

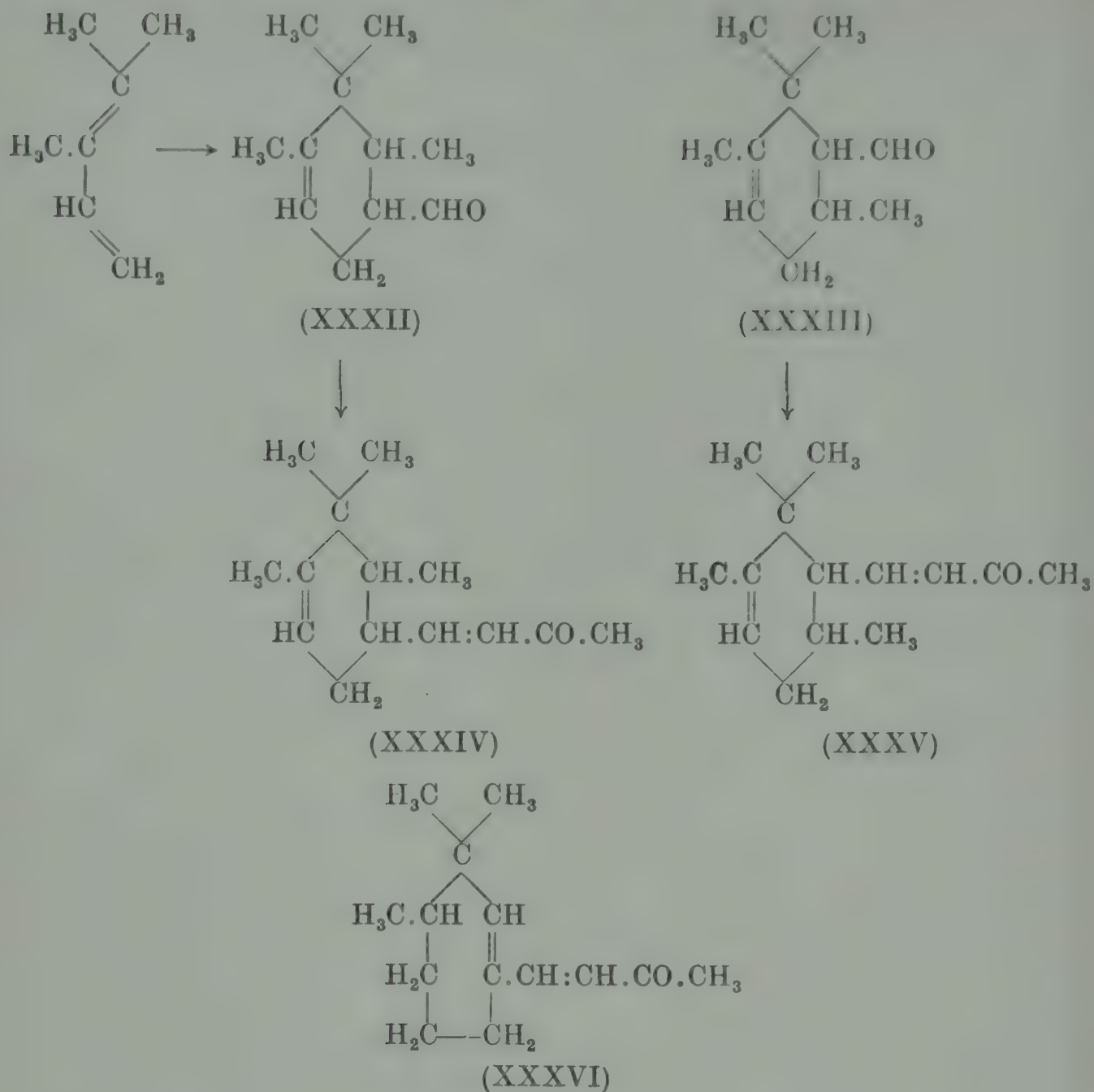
‡ Naves and Ardizio, *ibid.* p. 1280.

§ Naves, *ibid.* 1949, **32**, 611.

|| Winter, Schinz and Stoll, *ibid.* 1947, **30**, 2213; Rouvé and Stoll, *ibid.* p. 2216.

¶ *Ibid.* 1948, **31**, 2252, 2256.

** The term is unfortunate, in view of the alternative use of the prefix “*iso*” to indicate a definite stereochemical structure. †† *Helv. Chim. Acta*, 1948, **31**, 422.



The α - and γ -irones have the characteristic odour of natural irone, the α - being superior to the γ -. β -Irone, on the contrary, possesses an odour similar to the ionones. Although Ruzicka believes that there is no significant difference between the odours of α - and *iso*- α -irones, Naves* maintains that only α -irone has the characteristic odour of the iris.

The possible existence of a derivative of a dihydroirone in iris oil has been mentioned by Naves.†

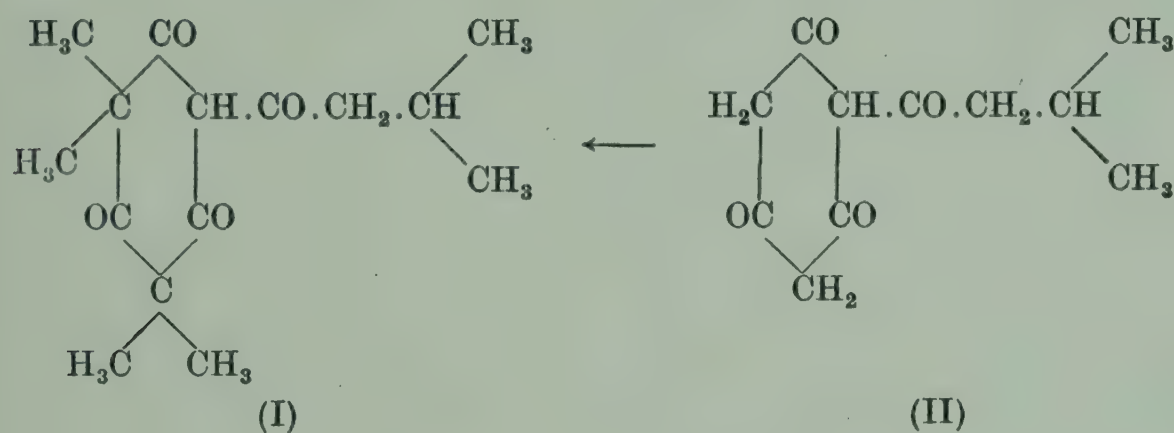
* *Helv. Chim. Acta*, 1948, 31, 893, 1103.

† *Ibid.* 1949, 32, 2171.

LEPTOSPERMONE

(Vol. I, p. 138)

The structure assigned to leptospermone (I) has been confirmed by synthesis* from phlorisovalerophenone (II), which on methylation with methyl iodide and potassium hydroxide gave an oil, b.p. 120–140° (bath temp.)/10 mm., from which the *anilino*-, m.p. 92°, *p-toluidino*-, m.p. 100°, and *benzylamino*-, m.p. 100°, derivatives were obtained, all of which were identical with similar derivatives obtained from the natural ketone. The synthetic ketone, regenerated from the benzylamino-derivative, had $n_D^{19.5^\circ}$ 1.5007, compared with $n_D^{19.5^\circ}$ 1.5000 for the natural compound.



LIMONENE

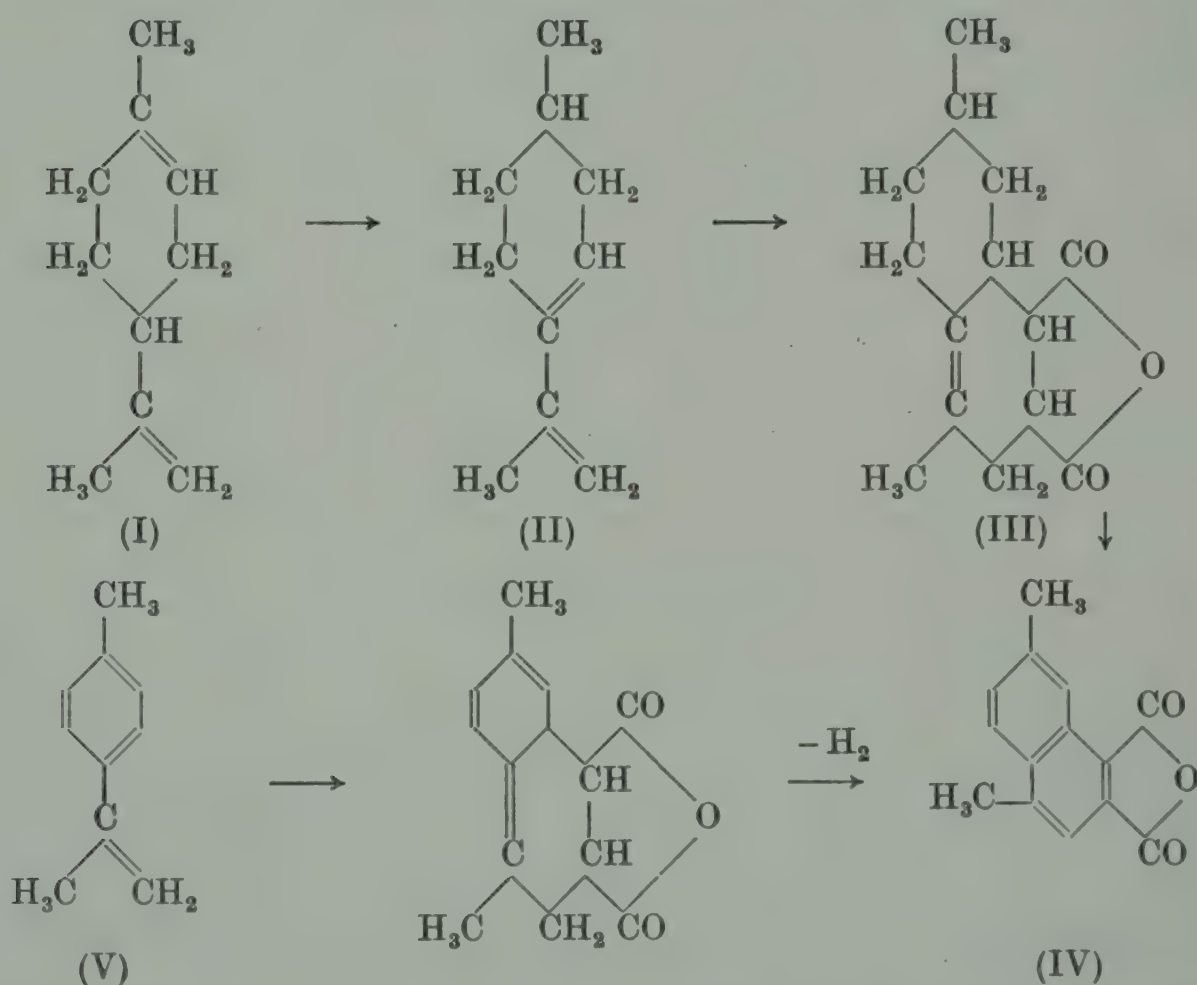
(Vol. I, p. 143)

In a study of the kinetics of the catalytic hydrogenation of terpenes over platinum or nickel catalysts, Smith, Fuzek and Meriwether† have shown that carvomenthene (menth-1-ene) is an intermediate in the hydrogenation of limonene; the double bond in the *isopropenyl* group is therefore preferentially reduced, as is already known to occur over copper (compare Vol. I, p. 153).

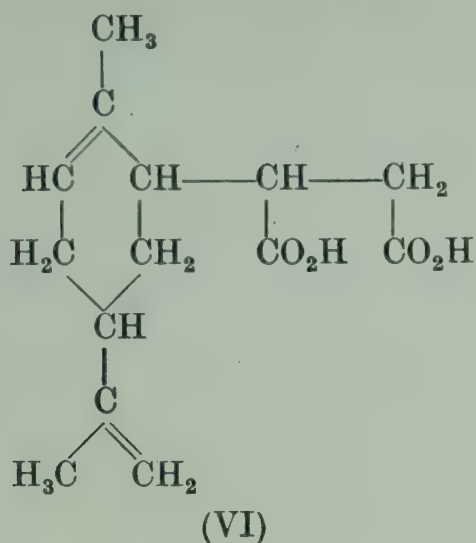
The reaction of limonene with maleic anhydride, to give an *acid*, $C_{14}H_{20}O_4$, m.p. 147° (compare Vol. I, p. 153) has been reinvestigated by Alder and Schmitz,‡ who have found that the yield can be improved by heating the components in benzene solution. It gives an *anhydride*, m.p. 52° (not 42°, as previously

* Briggs, Hassall and Taylor, *J.C.S.* 1948, p. 383.† *J. Amer. C.S.* 1949, 71, 3765.‡ *Annalen*, 1949, 565, 118.

recorded), a *dimethyl ester*, m.p. 79–80°, and a *dihydrazide*, m.p. 156°. When the ester is heated with sodium methoxide, and then saponified, an isomeric *acid*, m.p. 200°, is obtained, which is probably the *trans*-form of the original *cis*-acid. The latter, on dehydrogenation with bromine and acetic acid, followed by dehydration of the product with acetic anhydride, gave the *anhydride* of 4:7-dimethylnaphthalene-1:2-dicarboxylic acid (IV), m.p. 230°, the structure of which was confirmed by synthesis from maleic anhydride and 1-methyl-4-isopropenylbenzene (V). It appears very probable that the limonene (I) undergoes rearrangement to give *p*-mentha-3:8-diene (II) which then reacts with the maleic anhydride in the normal way to give (III).

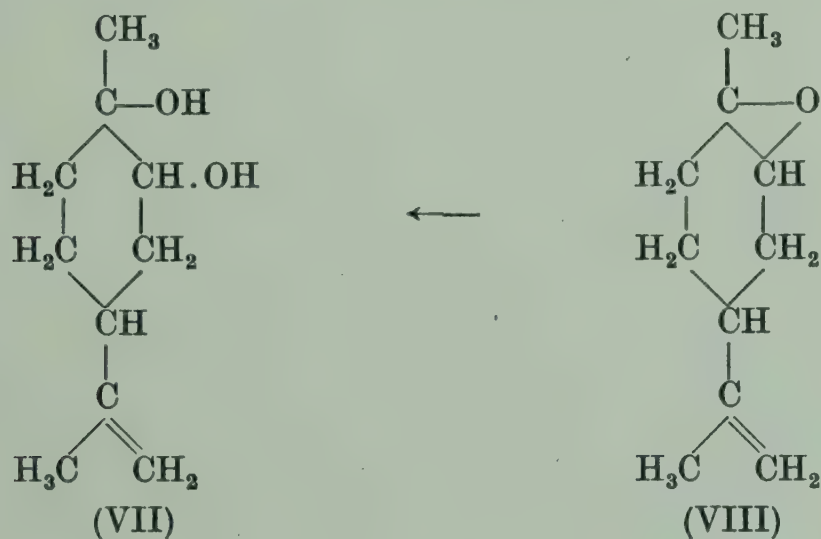


Alder and Schmitz have also found that, when limonene is heated with maleic anhydride at a higher temperature, an oil is obtained, which on saponification gives an *acid*, m.p. 181° (*dihydrazide*, m.p. 178°). This takes up four atoms of hydrogen on hydrogenation, and gives a *tetrahydro-acid*, m.p. 158°, suggesting that it contains two double bonds; furthermore, it cannot be converted into a *trans* form, and they suggest that it is probably of the type (VI).



The electrolytic oxidation of dipentene has been studied by Glasstone and Stanley.*

Schmidt,[†] in more recent investigations on the autoxidation of limonene, has confirmed the formation of carveol and carvone, and has also isolated crystalline *p*-menth-8-ene-1:2-diol (VII) for which he records m.p. 72.5–73.5°, $[\alpha]_D^{20} + 31^\circ$ (supercooled), $[\alpha]_D^{20} + 48^\circ$ (in acetone) for the anhydrous form, and m.p. 60°,



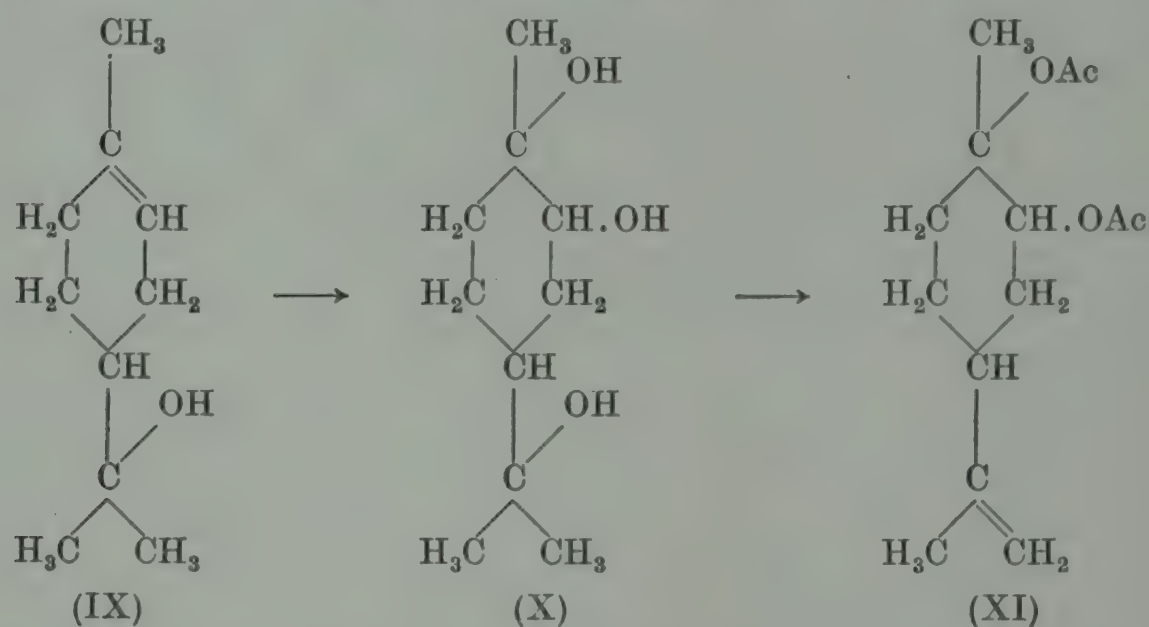
$[\alpha]_D^{20} + 33^\circ$ (in acetone) for the trihydrate. The glycol is identical with that obtained by hydration of limonene monoxide (VIII) (compare Vol. I, p. 155), and Schmidt considers that it is, consequently, the *cis*-form. This, however, is very improbable, since the opening of the oxide ring would be expected to be accompanied by an inversion of configuration, to give a *trans*-diol. The stereoisomeric glycol, m.p. 71–72°, $[\alpha]_D^{25} + 25^\circ$ (in acetone) is obtained by oxidation of terpineol (IX) with potassium permanganate to *p*-menthane-1:2:8-triol (X) (compare Vol. I,

* *Trans. Electrochem. Soc.* 1947, **92**, 543.

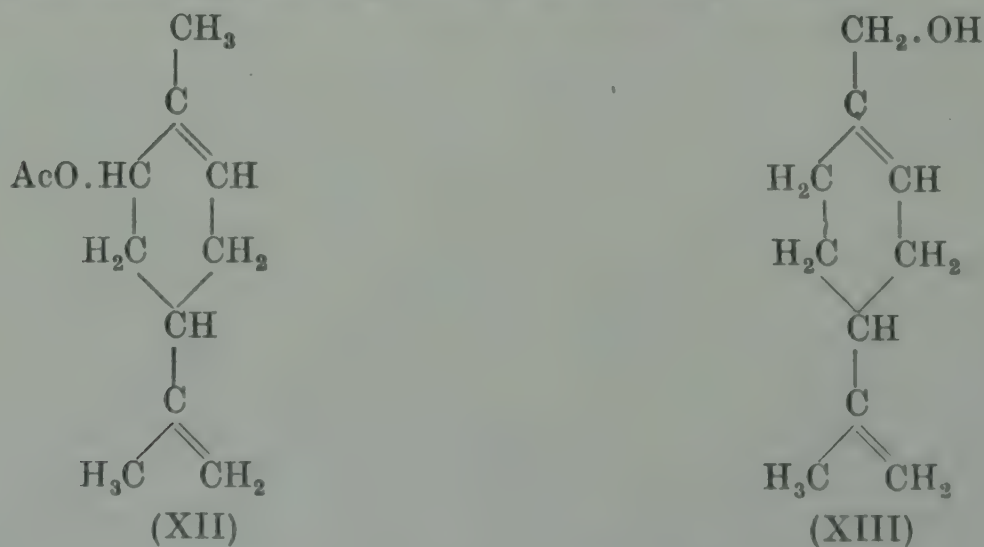
† *Chem. Ber.* 1949, **82**, 11.

p. 259), which on heating with acetic anhydride gives the diacetate (XI); saponification then yields the glycol. Schmidt considers this to be the *trans*-form, presumably because it differs from his "*cis*-" glycol. Permanganate oxidation, however, is recognised generally to give *cis*-diols, and Schmidt's stereochemical formulations require to be interchanged. Both forms of the diol, on treatment with formic acid, give *carvenone*.

Limonene reacts readily with primary alcohols, in the presence of sulphuric acid, to give ethers, mainly of α -terpineol.* Some-



what analogous to the autoxidation of limonene is the reaction which it undergoes with mercuric chloride, when 6-acetoxy-limonene (*carveol acetate*) (XII), is formed, b.p. 128–134°/14 mm., $d_4^{20^\circ}$ 1.0038, $n_D^{20^\circ}$ 1.4849, $\alpha_D^{20^\circ} + 5$.[†] Oxidation of *d*-limonene with selenium dioxide gives *d*-perillyl alcohol (XIII).[‡]



* Royals, *J. Amer. C.S.* 1949, **71**, 2568.

† Treibs and Bast, *Annalen*, 1949, **561**, 165.

‡ Schmidt, *Chem. Ber.* 1950, **83**, 200.

TERPINOLENE

(Vol. I, p. 165)

Smith, Fuzek and Meriwether* have studied the kinetics of the hydrogenation of terpinolene over platinum or Raney nickel; a mixture of menthenes, including *p-menth-3-ene*, is formed. Glasstone and Stanley† have investigated the electrolytic oxidation of terpinolene.

β-TERPINENE

(Vol. I, p. 186)

Calder and Carter‡ have reported the existence of *β*-terpinene in the oil from *Piltosporum tenuifolium*, one fraction of which gave a *tetrabromide*, m.p. 154–155°. Unfortunately, the amount was insufficient for complete characterisation.

PELLANDRENES

(Vol. I, p. 193)

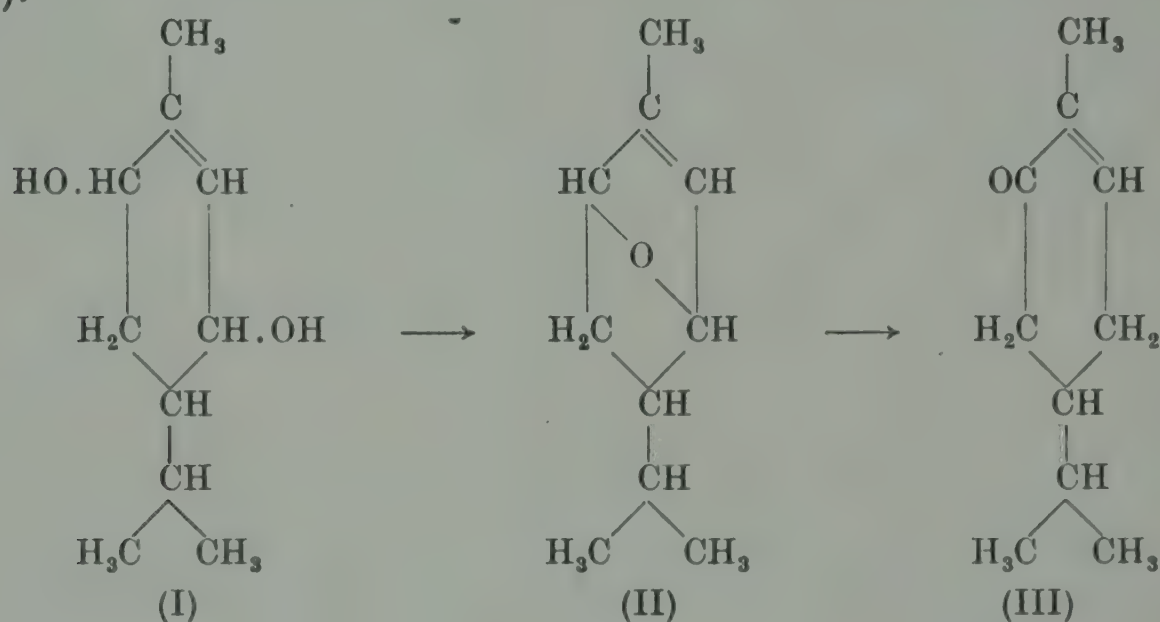
The highest rotation recorded for *d-α*-phellandrene is $\alpha_D^{16^\circ} + 86.4$.§ *l-β*-Phellandrene has been obtained in a higher state of purity by debromination of its *tetrabromide*.|| The following properties were recorded: b.p. 172–174°, $d_{15.5^\circ}^{15.5^\circ} 0.843$, $n_D^{20^\circ} 1.4826$, $[\alpha]_D - 74.4^\circ$. The molecular refraction (obs. 46.3, calc. 45.24) now shows the marked exaltation to be expected from the structure of the hydrocarbon (compare Vol. I, p. 205). A somewhat higher m.p., 109°, has also been found for the *nitrosochloride* (compare Vol. I, p. 209). When distilled at ordinary pressure, *β*-phellandrene undergoes polymerisation, with change in sign of optical rotation.

Acheson and West¶ have reinvestigated the product formed by reaction of *α*-phellandrene with *β*-naphthol (compare Vol. I, p. 203), and have obtained the same compound, m.p. 139–140°, $[\alpha]_D + 124^\circ$ (in alcohol), from *β*-phellandrene, though in this case

* *J. Amer. C.S.* 1949, **71**, 3765.† *Trans. Electrochem. Soc.* 1947, **92**, 543.‡ *J.S.C.I.* 1949, **68**, 355.§ Read and Storey, *J.C.S.* 1930, p. 2770.|| Berry, *Austral. Chem. Inst. J. and Proc.* 1947, **14**, 387.¶ *J.C.S.* 1949, p. 812.

partial isomerisation of the hydrocarbon to *l*-limonene occurs. When the compound is distilled at ordinary pressure it gives β -naphthol and α -terpinene. The same authors have recorded the infra-red spectra of α - and β -phellandrene.

In a renewed investigation of the autoxidation of α -phellandrene, Blumann and Ryder* have found that both the *cis*-, m.p. 54° (*hydrate*, m.p. 27°), $[\alpha]_D^{23} -33.6^\circ$, and the *trans*-form, m.p. 164 – 165° , of *p*-menth-1-ene-3:6-diol (I) are formed. When the *trans*-form is steam-distilled in 0.5 per cent sulphuric acid, it gives the *oxide* (II), $d_{15}^{22} 0.926$, $n_D^{20} 1.4775$, $[\alpha]_D -96^\circ$, which with more concentrated acid is isomerised to *carvotanacetone* (III).



$\Delta^{2:8(9)}$ -*p*-MENTHADIENE (ISOLIMONENE)

(Vol. I, p. 212)

Pigulevskii and Gorbunova† claim to have confirmed Tschugaev's isolation of isolimonene from the products of the pyrolysis of the methylxanthate of dihydrocarveol (compare Vol. I, pp. 213, 285), and that the Raman spectrum agrees with the suggested structure.

* *J.C.S.* 1949 p. 2040.

† *Amer. Chem. Abstr.* 1947, 41, 6551.

MENTHOL

(Vol. I, p. 230)

A new method for the commercial production of *dl*-menthol has been described by Brode and van Dolah.* This is based on the discovery that the mixture of stereoisomeric menthols, obtained by the reduction of thymol, contains a higher proportion of the desired *dl*-menthol when copper chromite, rather than nickel, is used as a catalyst (compare Vol. I, p. 233).

The separation of menthol and *neomenthol* can be accomplished by chromatography on alumina, the *trans*-alcohol (menthol) being more strongly adsorbed.† Borneol and *iso*-borneol are similarly separated.

Jackman, Macbeth and Mills‡ have investigated the reduction of menthone to menthol by the Ponndorf method (compare Vol. I, p. 237) and have confirmed that the product contains at least 70 per cent of *neomenthol*. Even higher proportions of this stereoisomer are formed when the aluminium *isopropoxide* is replaced by the aluminium derivatives of more sterically hindered secondary alcohols, such as methyl-*tert*.-butylcarbinol.

CARVOMENTHOL

(Vol. I, p. 250)

Although Johnston and Read^{||} have emphasised that the final allocations of configurations to the stereoisomeric carvomenthols can only be safely made when the alcohols have been more satisfactorily characterised, and their relative rates of esterification determined, it is nevertheless possible, on the assumption that the configurations of the carveols and carvomenthones (based

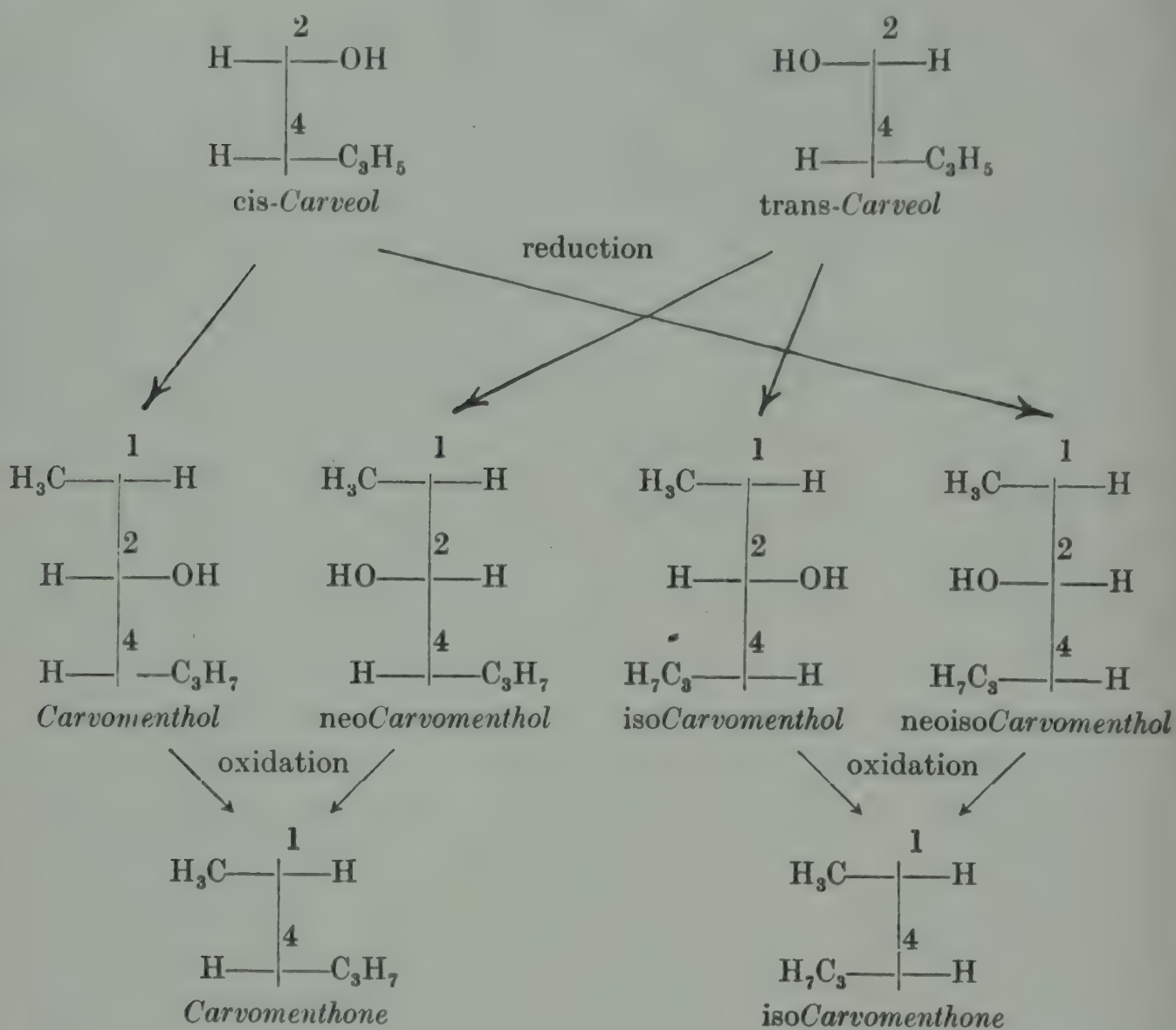
* *Ind. Eng. Chem.* 1947, **39**, 1157.

† Vavon and Gastambide, *Compt. rend.* 1948, **226**, 1201.

‡ *J.C.S.* 1949, p. 2641.

^{||} *J.C.S.* 1935, p. 1138.

only on the Auwers-Skita rule) are correct, to arrive at the following formulae:



This is based on the known relationships between the carvomenthols and the other compounds involved (see also p. 520).

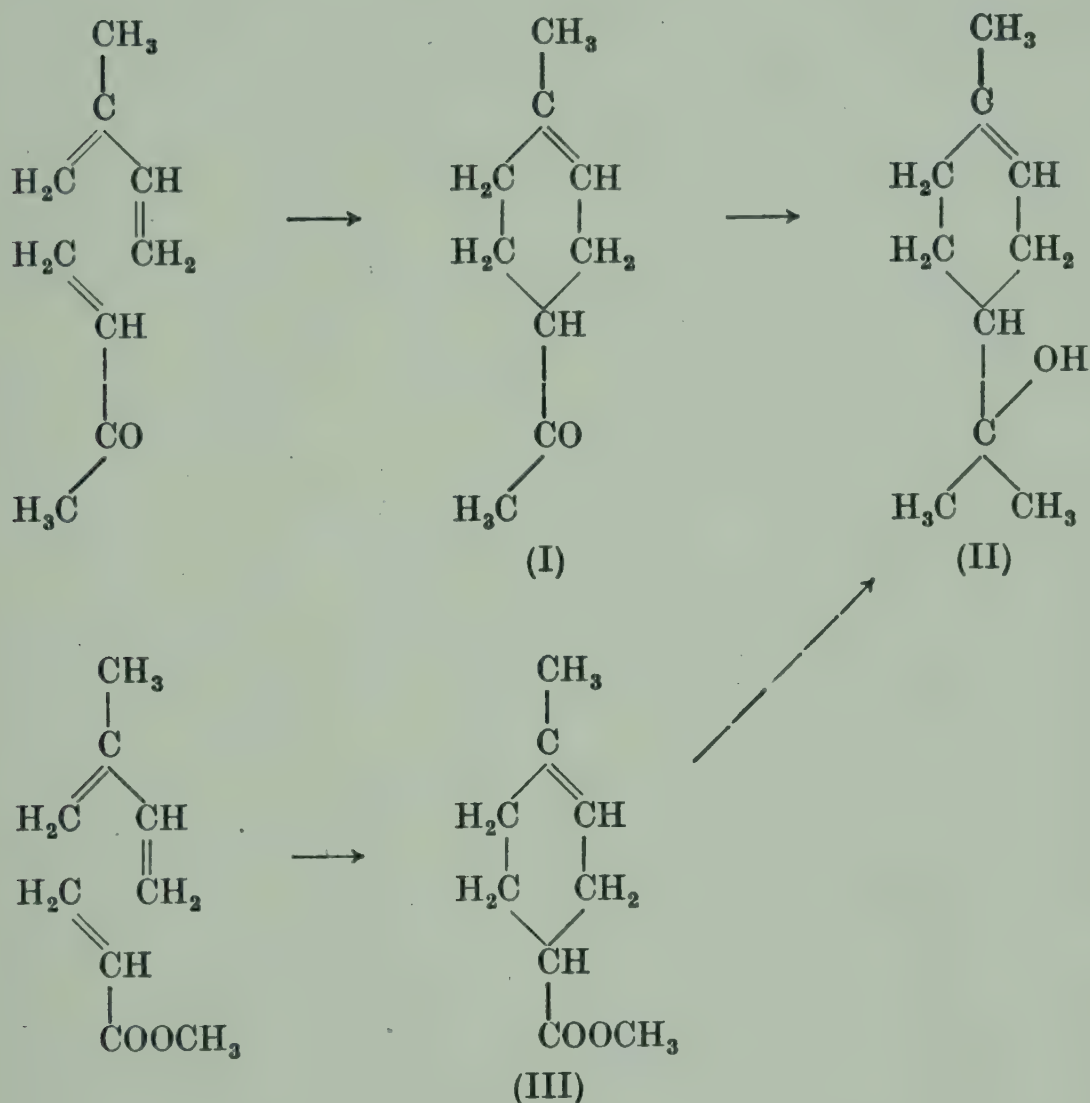
α -TERPINEOL

(Vol. I, p. 256)

A simple synthesis of α -terpineol has been described by Alder and Vogt.* Condensation of isoprene and methyl vinyl ketone gave 4-methyl- Δ^3 -tetrahydroacetophenone (I) which on treatment

* *Annalen*, 1949, 564, 109.

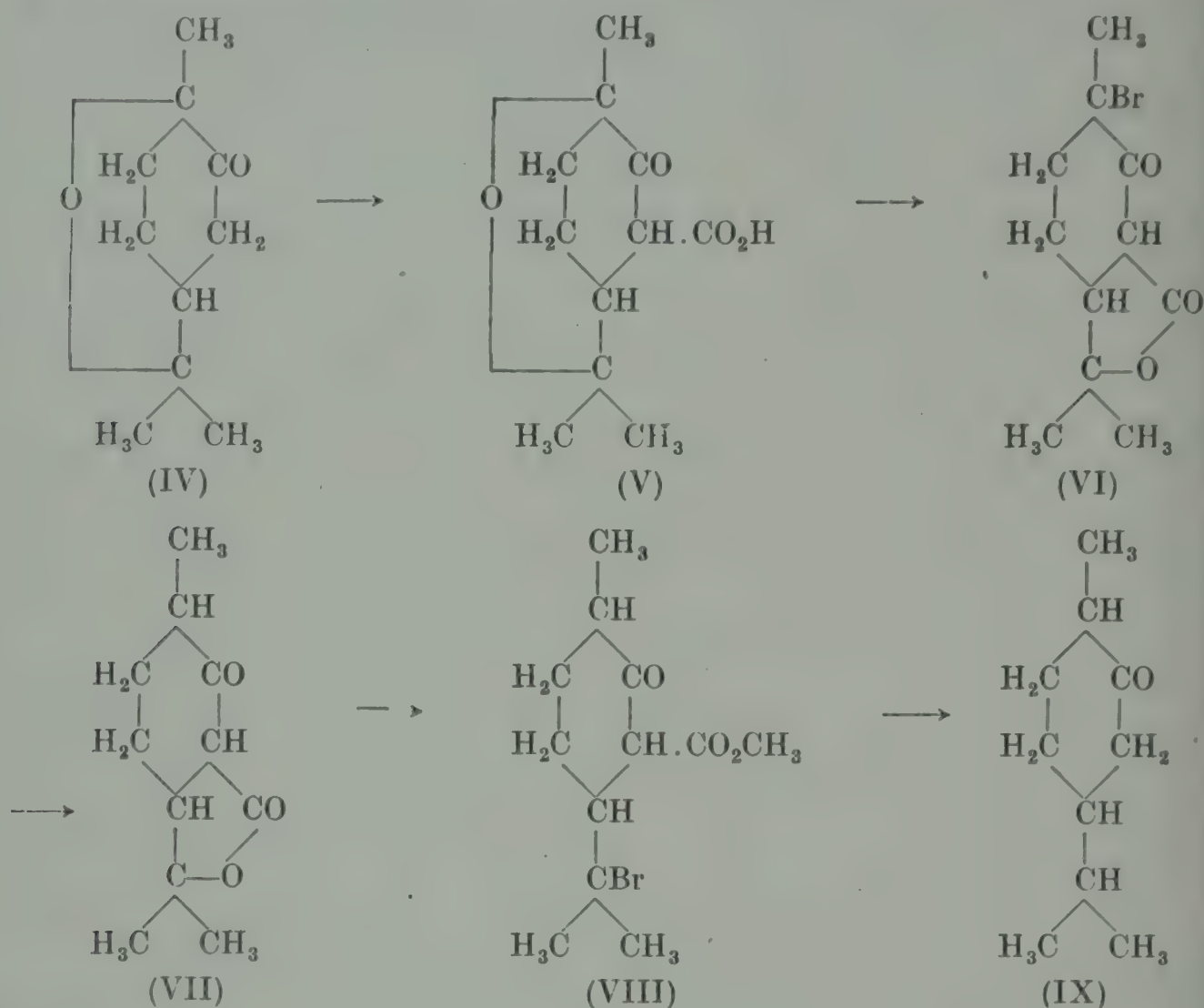
with methylmagnesium bromide gave *dl*- α -terpineol (II). An alternative synthesis involved reaction of methylmagnesium bromide with methyl 4-methyl- Δ^3 -tetrahydrobenzoate (III), derived by condensation of isoprene with methyl acrylate.



Gandini* has continued his studies on the properties of *keto-cineole* (IV) (compare Vol. I, p. 265). Treatment with sodamide and carbon dioxide gave the 3-carboxylic acid (V), m.p. 103°, which with hydrogen bromide underwent ring-fission to give the lactone (VI) of 1-bromo-8-hydroxycarvomenthone-3-carboxylic acid, m.p. 148°. Debromination with zinc and ethanol gave (VII), which with hydrogen bromide in methanol gave methyl 8-bromo-carvomenthone-3-carboxylate (VIII). Debromination, followed by

* *Gazzetta*, 1940, 70, 438.

saponification, and decarboxylation of the resulting β -keto-acid, gave *carvomenthone* (IX).



γ -TERPINEOL

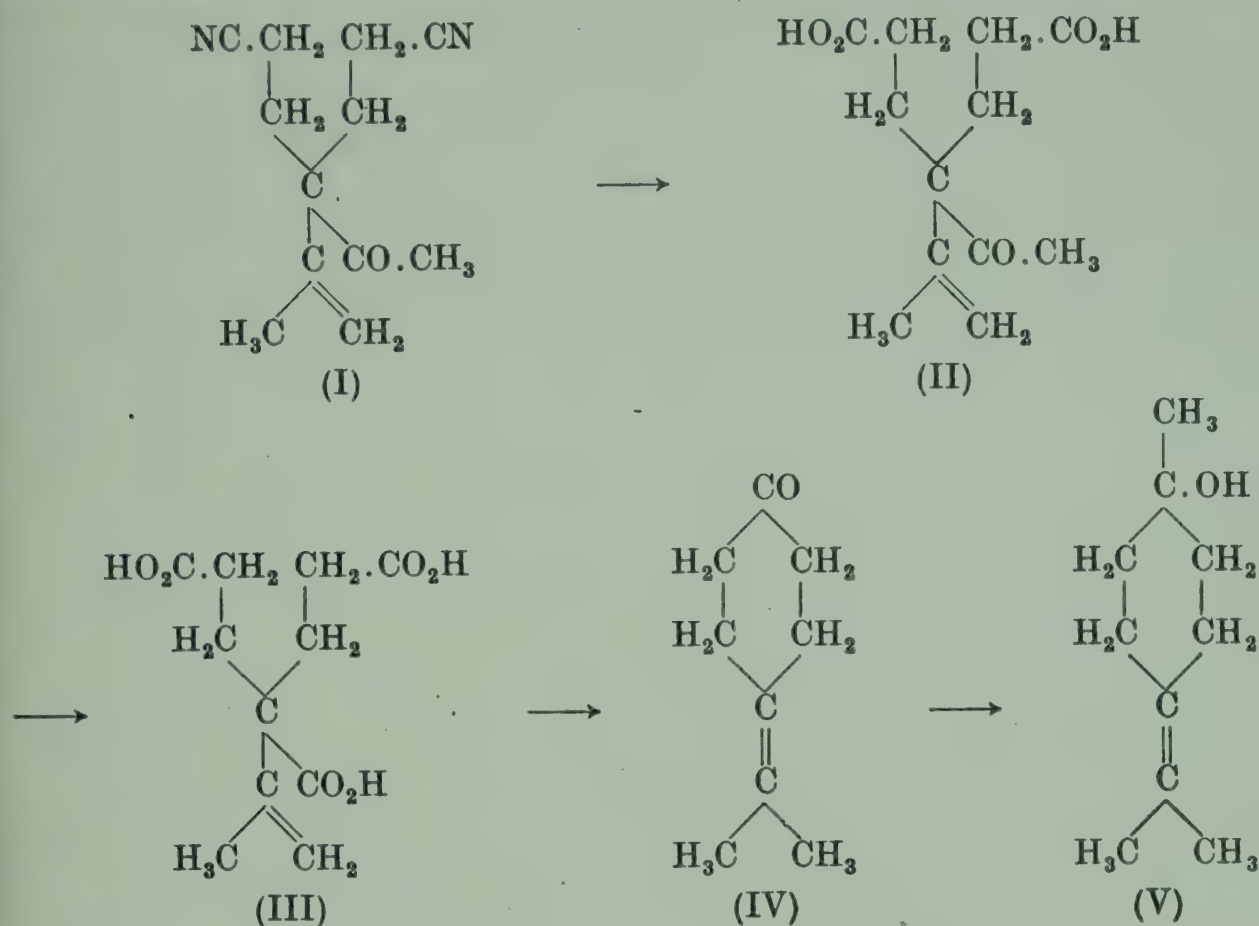
(Vol. I, p. 271)

The following synthesis has been carried out by Frank and McPherson.* Condensation of mesityl oxide and acrylonitrile, by the method of Bruson and Riener[†] gave the nitrile (I), from which, on hydrolysis, the acid (II) was obtained, and converted by hypochlorite oxidation into γ -carboxy- γ -isopropenylpimelic acid (III), m.p. 158–160°. When this was heated with barium carbonate above 300°, cyclisation, decarboxylation, and isopropenyl-isopropylidene isomerisation occurred, to give 4-isopropylidenecyclohexanone (IV), b.p. 54°/1 mm., d_{20}^{20} 0.959, n_D^{20} 1.4817. The structure of this ketone was confirmed by ozonolysis, when it gave cyclohexa-1:4-dione and acetone; only a trace of

* *J. Amer. C.S.* 1949, 71, 1387.

† *Ibid.* 1943, 65, 18.

formaldehyde was formed. When treated with methylmagnesium iodide it gave γ -terpineol (V), m.p. 63–67°, in rather poor yield.



TERPINEN-4-OL

(Vol. I, p. 275)

The *l*-alcohol occurs in the oils from *Eucalyptus australiana*, var. A.* On hydrogenation it gives one stereoisomer, m.p. 53° (*phenylurethane*, m.p. 140°) of *p*-menthan-4-ol.†

DIHYDROCARVEOL

(Vol. I, p. 280)

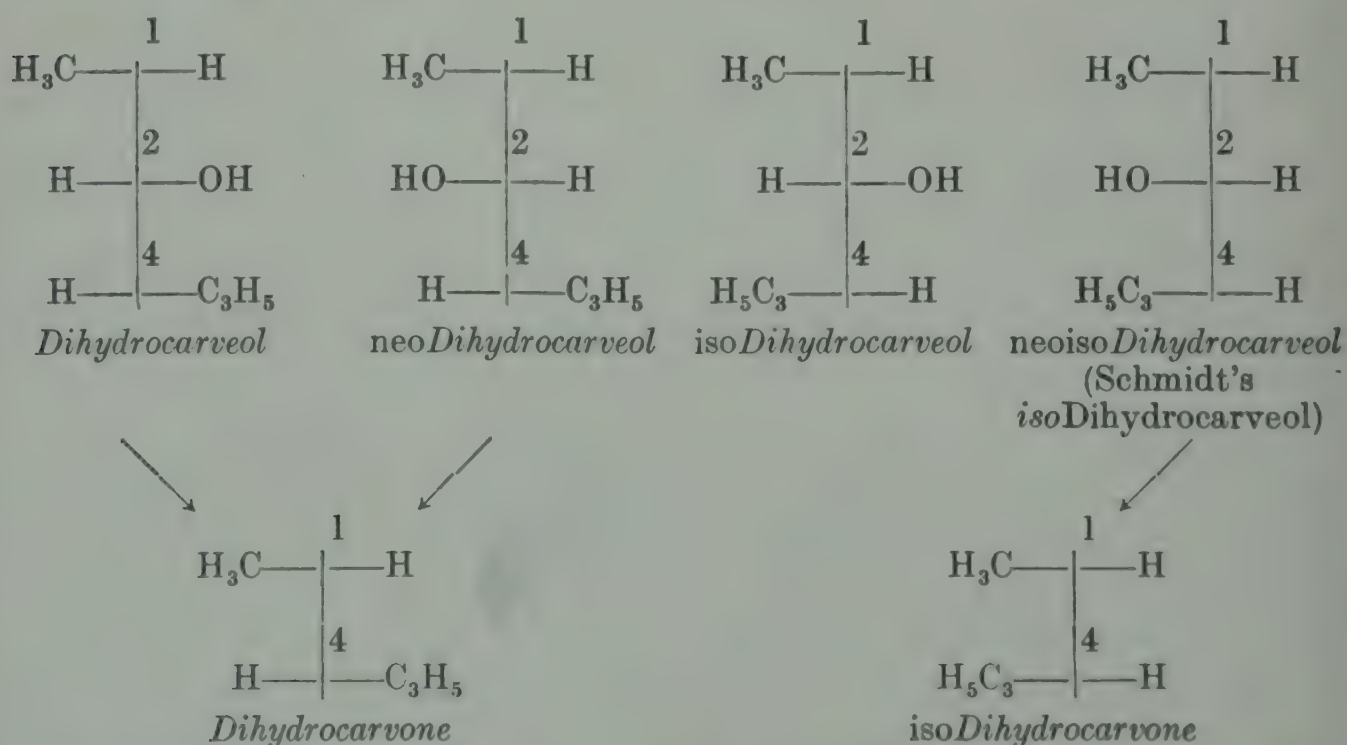
By fractional distillation of oil of caraway, Schmidt‡ has obtained not only the already known *d*- and *l*-neodihydrocarveols (*hydrogen phthalates*, m.p.s 72–73° and 96–97° respectively), but also a new stereoisomer, *l*-isodihydrocarveol, m.p. 38–39°, $[\alpha]_D -28^\circ$ (in alcohol), $d_{15}^\circ 0.942$, $n_D^{20} 1.4816$ (*hydrogen phthalate*, m.p. 104–105°; *p*-nitrobenzoate, m.p. 45–46°). On oxidation, the

* Penfold and Morrison, *J. Proc. Roy. Soc. New South Wales*, 1935, **69**, 111.

† Naves, *Helv. Chim. Acta*, 1948, **31**, 1937.

‡ *Chem. Ber.* 1950, **83**, 193.

d- and *l*-neodihydrocarveols both give *l*-dihydrocarvone, b.p. $220^{\circ}/750$ mm., $d_{15}^{15^{\circ}} 0.929$, $n_D^{20^{\circ}} 1.4735$, $\alpha_D -15.6^{\circ}$ (semicarbazone, m.p. 189° ; oxime, m.p. $88-89^{\circ}$), whilst *l*-isodihydrocarveol gives *l*-isodihydrocarvone, b.p. $221^{\circ}/750$ mm., $d_{15}^{15^{\circ}} 0.942$, $n_D^{20^{\circ}} 1.4742$, $\alpha_D -23.7^{\circ}$ (semicarbazone, m.p. 179°). On the basis of the Auwers-Skita rule, these two ketones are allocated *trans*- and *cis*-structures respectively. Furthermore, since the acetate of *d*-dihydrocarveol is saponified much more rapidly than that of *l*-neo-dihydrocarveol, these two stereoisomers are probably *trans*- and *cis*-forms, respectively, with regard to the configurations about carbon atoms 1 and 2. On the assumption that the carvomenthols have been correctly formulated (p. 516), this conclusion is in accord with the previous known fact that on hydrogenation these two dihydrocarveols give carvomenthol and neocarvomenthol respectively (Vol. I, p. 283). Schmidt did not allocate any configuration to his isodihydrocarveol, but since he showed that on hydrogenation it gave a carvomenthol which from its properties (*p*-nitrobenzoate, m.p. $54-55^{\circ}$; 3:5-dinitrobenzoate, m.p. 71°) is clearly *neoisocarvomenthol* (compare Vol. I, p. 252) the new dihydrocarveol should evidently be named *neoisodihydrocarveol*. The following structures can therefore be deduced:



On hydration, *d*-, *l*-neo-, and *l*-neoisodihydrocarveols give the corresponding stereoisomers, m.p.s $112-113^{\circ}$, $158-159^{\circ}$, and $86-87^{\circ}$ respectively, of *p*-menthane-2:8-diol (compare Vol. I, p. 284).

PHELLANDRAL

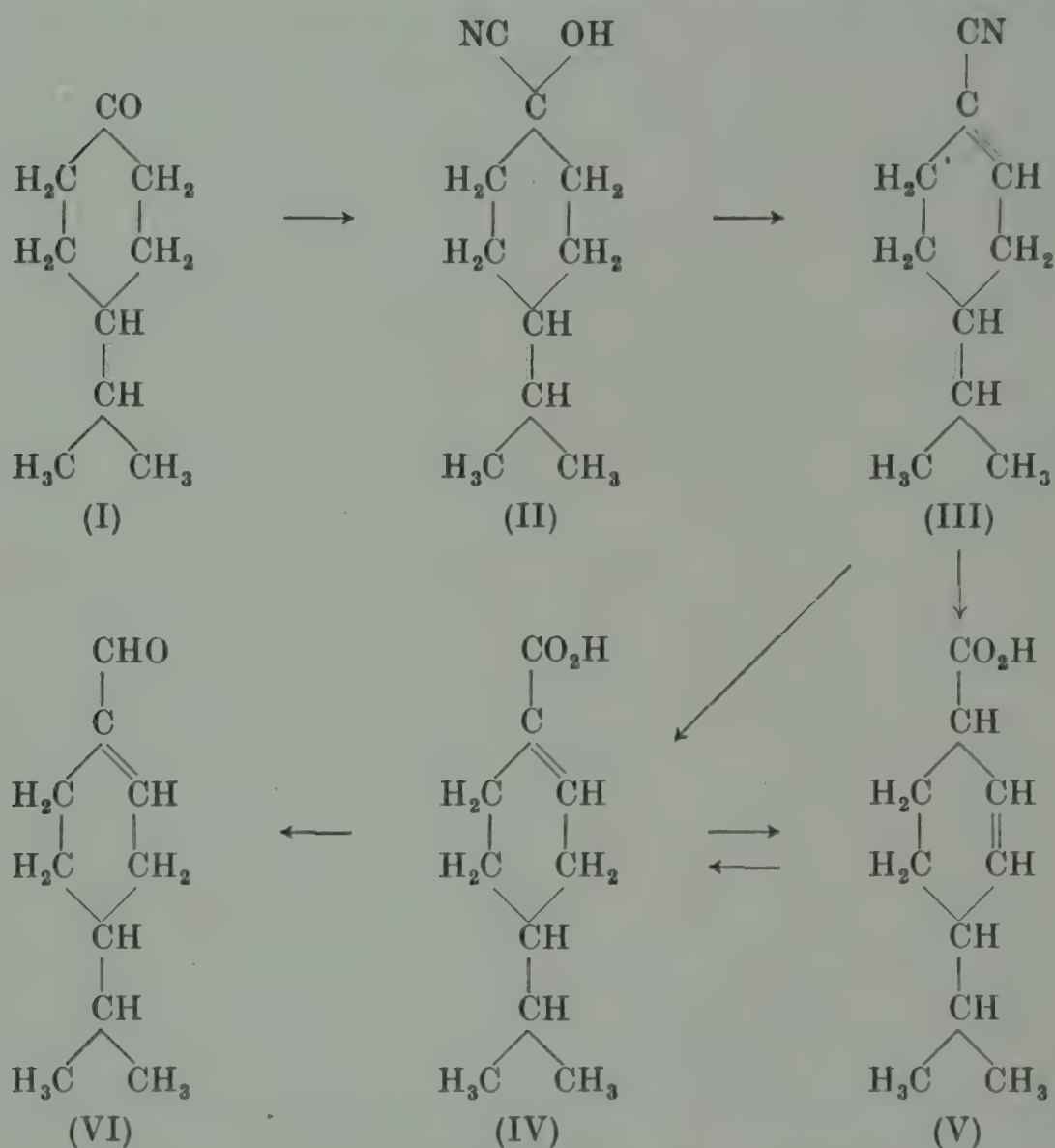
(Vol. I, p. 308)

The structure of phellandral has now been confirmed by synthesis.* *p*-isoPropylphenol was hydrogenated over Raney nickel to give 4-isopropylcyclohexanol, from which 4-isopropylcyclohexanone (I) was obtained by oxidation with chromic acid. The cyanohydrin (II) from this ketone was then converted, by pyrolysis of its acetate, into 4-isopropyl-1-cyanocyclohexene (III), the position of the double bond being confirmed by observation of the characteristic absorption spectrum of an $\alpha\beta$ -unsaturated nitrile. Hydrolysis of the nitrile, under either acid or alkaline conditions, gave not only the corresponding acid (IV) (*dl*-phellandric acid), but also the $\beta\gamma$ -unsaturated isomer (V). Some pure $\beta\gamma$ -unsaturated acid was isolated from the products of acid hydrolysis, but with alkaline hydrolysis an inseparable mixture was obtained; the proportion of (IV) in this, however, was increased by heating with ethanolic sodium ethoxide, and in this way a quantity of *dl*-phellandric acid was obtained, m.p. 142–144° (*anilide*, m.p. 131–132°). Resolution with quinine, followed by phenylethylamine, gave *d*-phellandric acid, m.p. 143–144°, $[\alpha]_D^{26} + 112^\circ$ in methanol, the physical constants being in excellent agreement with the acid derived from *d*-phellandral (compare Vol. I, p. 310). The synthetic *dl*-phellandric acid was reduced by the von Braun method,† through the phenylimido-chloride, and gave *dl*-phellandral (VI), b.p. 103–105°/9 mm., $d_{20}^{20} 0.944$, $n_D^{20} 1.4896$ (*oxime*, m.p. 76–77°; *semicarbazone*, m.p. 199.5–200.5°; 2:4-dinitrophenylhydrazone, m.p. 194.5–196°).

When phellandral is reduced by the Ponndorf method it gives 1-phellandrol, b.p. 114°/5 mm., $d_4^{30} 0.9252$, $n_D^{20} 1.4826$, $\alpha_D^{20} - 100^\circ$. The *p*-nitrobenzoate has m.p. 67°, $[\alpha]_D^{16} - 56.6^\circ$; the *hydrogen phthalate* m.p. 74°, $[\alpha]_D - 54.4^\circ$; the *phenylurethane* m.p. 79°, $[\alpha]_D^{16} - 60.1^\circ$; the α -*naphthylurethane* m.p. 69.5°, $[\alpha]_D^{16} - 52.6^\circ$; and the 3:5-dinitrobenzoate m.p. 57.5°, $[\alpha]_D^{15} - 49.8^\circ$, all rotations being in chloroform solution.‡ In the reduction, some *diphellandryl ether* is also formed, b.p. 170–180°/1 mm., d_4^{19}

* Frank, Berry and Shotwell, *J. Amer. C.S.* 1949, 71, 3889.† *Ber.* 1934, 67, 269.‡ Human, Macbeth and Rodda, *J.C.S.* 1949, p. 350.

0.9337, n_D^{19} 1.4986, $[\alpha]_D -71.4^\circ$. It has also been found* that *dihydrophellandral*, obtained by hydrogenation of phellandral over platinum (compare Vol. I, p. 310), gives a *p*-nitrophenylhydrazone, m.p. 161° , and two semicarbazones, m.p.s 173° and 139° . The dihydrophellandral must be a mixture of *cis*- and



trans-forms, since on reduction by the Ponndorf method, or by hydrogenation over nickel or platinum, it gives a mixture of *cis*-dihydrophellandrol (*p*-nitrobenzoate, m.p. $54-55^\circ$; α -naphthylurethane, m.p. 78° ; 3:5-dinitrobenzoate, m.p. $71-72^\circ$) and *trans*-dihydrophellandrol (3:5-dinitrobenzoate, m.p. 95°). Since, however, the aldehyde recovered from each of the two semicarbazones mentioned above, on oxidation, gives *trans*-hexahydrocuminic acid in each case, it is concluded that the semicarbazones are not derivatives of the two possible forms of the aldehyde, but are both derivatives of *trans*-dihydrophellandral. This argument

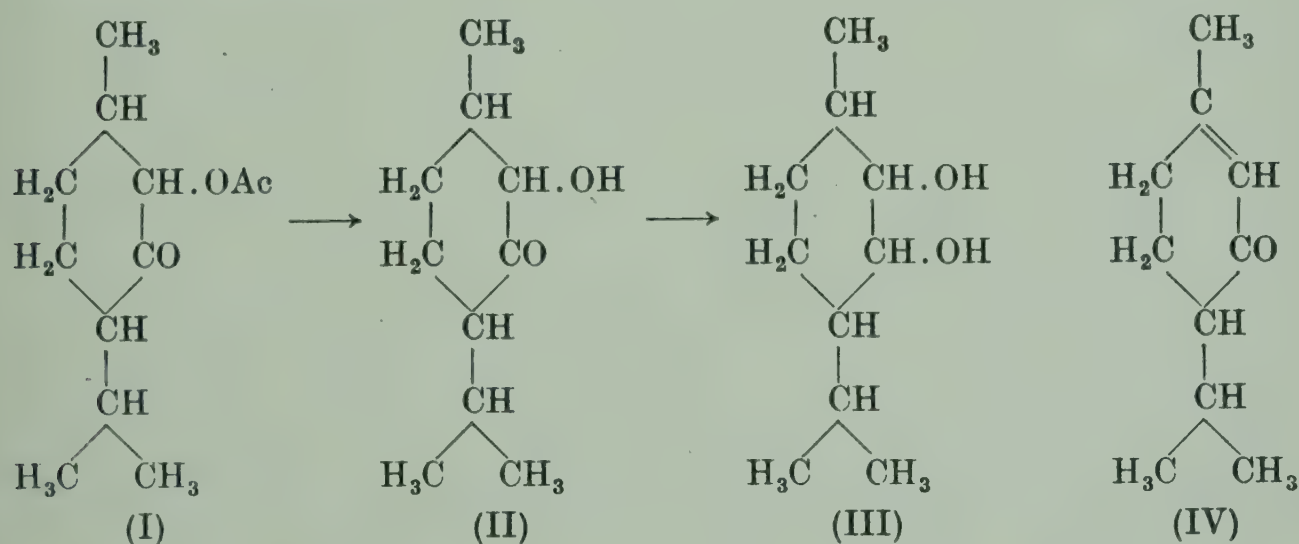
* Human, Macbeth and Rodda, *J.C.S.* 1949, p. 350.

is evidently based on the assumption, not necessarily correct, that no isomerisation occurs during the hydrolysis of the semicarbazones.

MENTHONE

(Vol. I, p. 314)

According to Naves* the oil from *Micromeria abyssinica* (Hochst.) Benth. consists mainly of a mixture of *d*-isomenthone and *d*-pulegone. He finds m.p. 126–128° for the semicarbazone of isomenthone, raised on remelting to 150–175°. There are considerable discrepancies in the recorded values for the melting-point of this derivative, which can probably exist in several modifications.† The figure 264° recorded in the table (Vol. I, p. 241) is erroneous; 164° was given by Zeitschel and Schmidt.‡ Badoche§ gives m.p.s 193° and 136° for the semicarbazones of *l*-menthone and *d*-isomenthone, respectively, and has studied their interconversion.



When menthone is treated with mercuric acetate in acetic acid solution it gives 2-acetoxymenthone (I), b.p. 134°/14 mm., d_4^{20} 1.019, n_D^{20} 1.4583, α_D^{20} -31.3° , and thence, by saponification, menthan-2-ol-3-one (II) (compare Vol. I, p. 419), b.p. 111–112°/14 mm., d_4^{20} 0.9883, n_D^{20} 1.4636, α_D^{20} $+1.1^\circ$, is obtained. This, on reduction, gives a mixture of glycols from which a solid isomer, m.p. 92°, of menthane-2:3-diol (III) is obtained.^{||} This is

* *Helv. Chim. Acta*, 1948, **31**, 932.

† Compare Hughesdon, Smith and Read, *J.C.S.* 1923, **123**, pp. 2920, 2921.

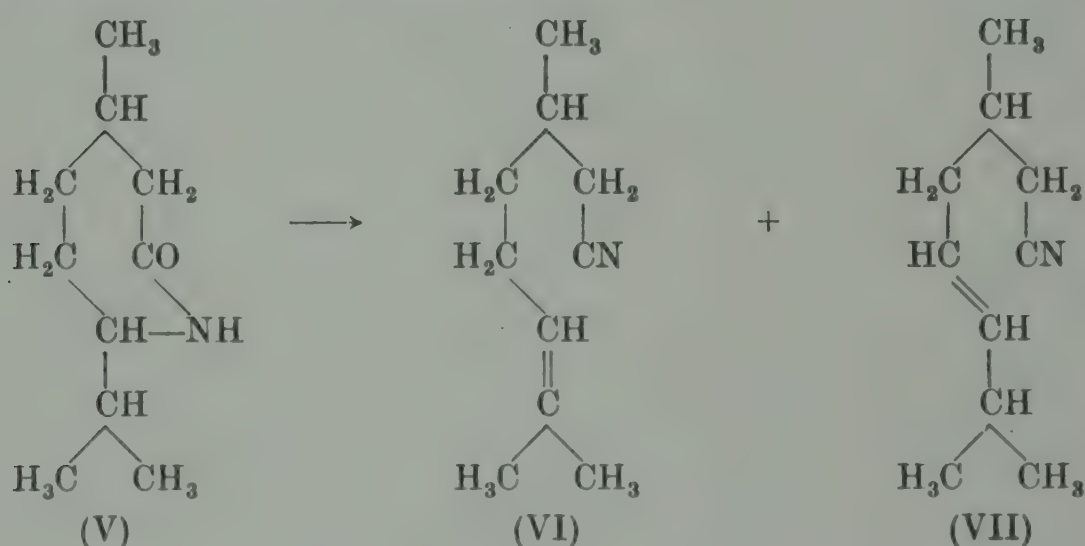
‡ *Ber.* 1926, **59**, 2298.

§ *Ann. Chim.* 1949 [xii], **4**, 449.

^{||} Treibs and Bast, *Annalen*, 1949, **561**, 165.

probably identical with the glycol obtained by reduction of diosphenol (see Vol. I, p. 418). The corresponding caproyloxy-menthone, when heated, loses caproic acid and gives *piperitone* (IV).

The problem of the identity of the nitrile formed by the action of phosphorus pentachloride on menthone isoxime (V) (compare Vol. I, p. 323) has been investigated by Herschmann,* who has shown that the product is a mixture of *citronellonitrile* (VI), b.p. 95.5–96°/10 mm., $d_4^{20^\circ}$ 0.8467, n_D 1.4491, $[\alpha]_D^{20^\circ}$ -10° , and *mentho-citronellonitrile* (VII), b.p. 91.5–92°/11 mm., $d_4^{20^\circ}$ 0.8332, n_D 1.4400, $[\alpha]_D^{20^\circ}$ -14° . The structure of the latter is confirmed by its Raman spectrum, and also by reduction of the corresponding acid to dihydrocitronellic acid, and by ozonisation to isobutyraldehyde and β -methylglutaric acid.†



CARVOMENTHONE

(Vol. I, p. 327)

Treibs and Bast‡ have shown that by reaction of carvomenthone with mercuric acetate, the 3-acetoxy-derivative is formed, which on hydrolysis yields *p-menthan-3-ol-2-one*, b.p. 118°/14 mm., $d_4^{20^\circ}$ 0.9845, $n_D^{20^\circ}$ 1.4564, $\alpha_D^{20^\circ}$ -42° .

* *Helv. Chim. Acta*, 1949, **32**, 2537.

† The systematic names given to the nitriles in this paper are erroneous.

‡ *Annalen*, 1949, **561**, 165.

CRYPTONE

(Vol. I, p. 334)

According to Berry* cryptone gives an unstable bisulphite compound from which it can be regenerated with alkali.

In a renewed investigation of *cryptol* (compare Vol. I, p. 336) obtained by reduction of cryptone with aluminium isopropoxide, Gillespie, Macbeth and Mills† have succeeded in separating the product, by fractional crystallisation of the 3:5-dinitrobenzoate, into *l-trans-cryptol* and *d-cis-cryptol*. The physical constants of these stereoisomers, and of some derivatives, are given in the table.

	<i>cis</i> -	<i>trans</i> -
B.p.	70°/1.5 mm.	60°/0.5 mm.
$d_4^{30^\circ}$	0.9293	0.9261
$n_D^{20^\circ}$	1.4811	1.4793
α_D in chloroform	+74°	-118°
Allophanate, m.p.	166-168°	196-197°
Urethane, m.p.	118-119°	—
Phenylurethane, m.p.	56.5-57.5°	106-107°
α -Naphthylurethane, m.p.	98-99°	118.5-119.5°
p-Nitrobenzoate, m.p.	48.5-49.5°	—
3:5-Dinitrobenzoate, m.p.	112.5-113.5°	120-121°
Hydrogen phthalate, m.p.	68.5-70°	85-86°

The *cis*- and *trans*-configurations are supported by the observation that the *cis*-alcohol on hydrogenation gives the already known *cis*-dihydrocryptol (compare Vol. I, p. 337). The same authors reported that *l*-cryptone gives an *oxime*, m.p. 56.5-57.5°, $[\alpha]_D^{21^\circ} - 106^\circ$ in chloroform, but were unable to confirm the high value of $[\alpha]_D - 119.3^\circ$ (in alcohol) previously reported for the ketone itself; for what they considered to be optically pure *l*-cryptone, prepared from the pure cryptols in several ways, they recorded $\alpha_D^{20.5^\circ} - 65.9^\circ$, $[\alpha]_D^{20^\circ} - 91.7^\circ$ (in alcohol).

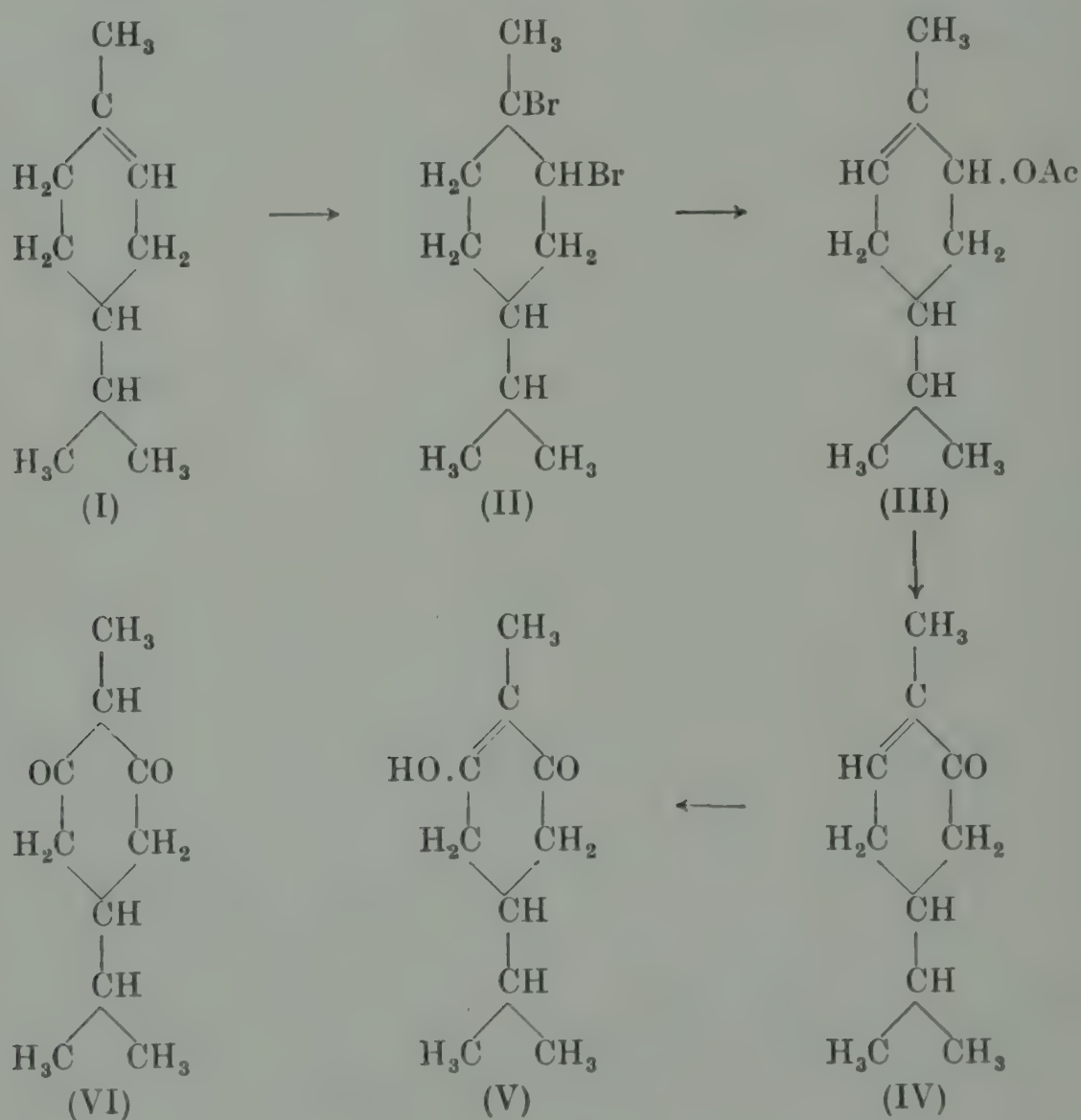
CARVOTANACETONE

(Vol. I, p. 338)

Two methods for the formation of carvotanacetone from *carvomenthene* (Δ^1 -menthene) (I) have been described. Dupont, Dulou

* *Austral. Chem. Inst. J. and Proc.* 1947, 14, 387.† *J.C.S.* 1948, p. 996.

and Bulteau* converted the hydrocarbon into the *dibromide* (II), which on treatment with sodium acetate gave the *acetate* (III) of carvotanacetol; saponification and oxidation then gave carvotanacetone (IV). Treibs and Bast† treated the menthene (I) with mercuric acetate and obtained the acetate (III) directly, which then gave carvotanacetone as above. The latter authors also found that, on oxidation in alkaline solution with hydrogen peroxide, the *hydroxycarvotanacetone* (V), m.p. 181°, was obtained; this substance is of interest as being an enolic form of *menthans-2:6-dione* (VI).



CARVENONE

(Vol. I, p. 345)

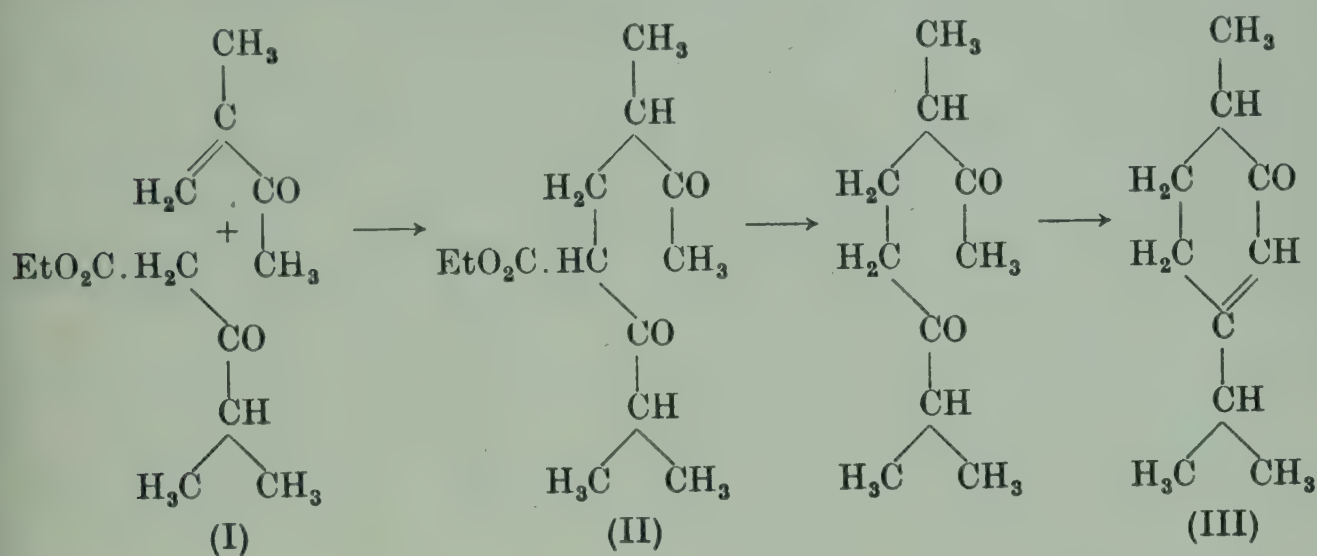
Henecka‡ has described a synthesis of the ketone from *ethyl isobutyrylacetate* (I), which on condensation with methyl iso-

* *Bull. Soc. chim.* 1948 [v], 15, 195.

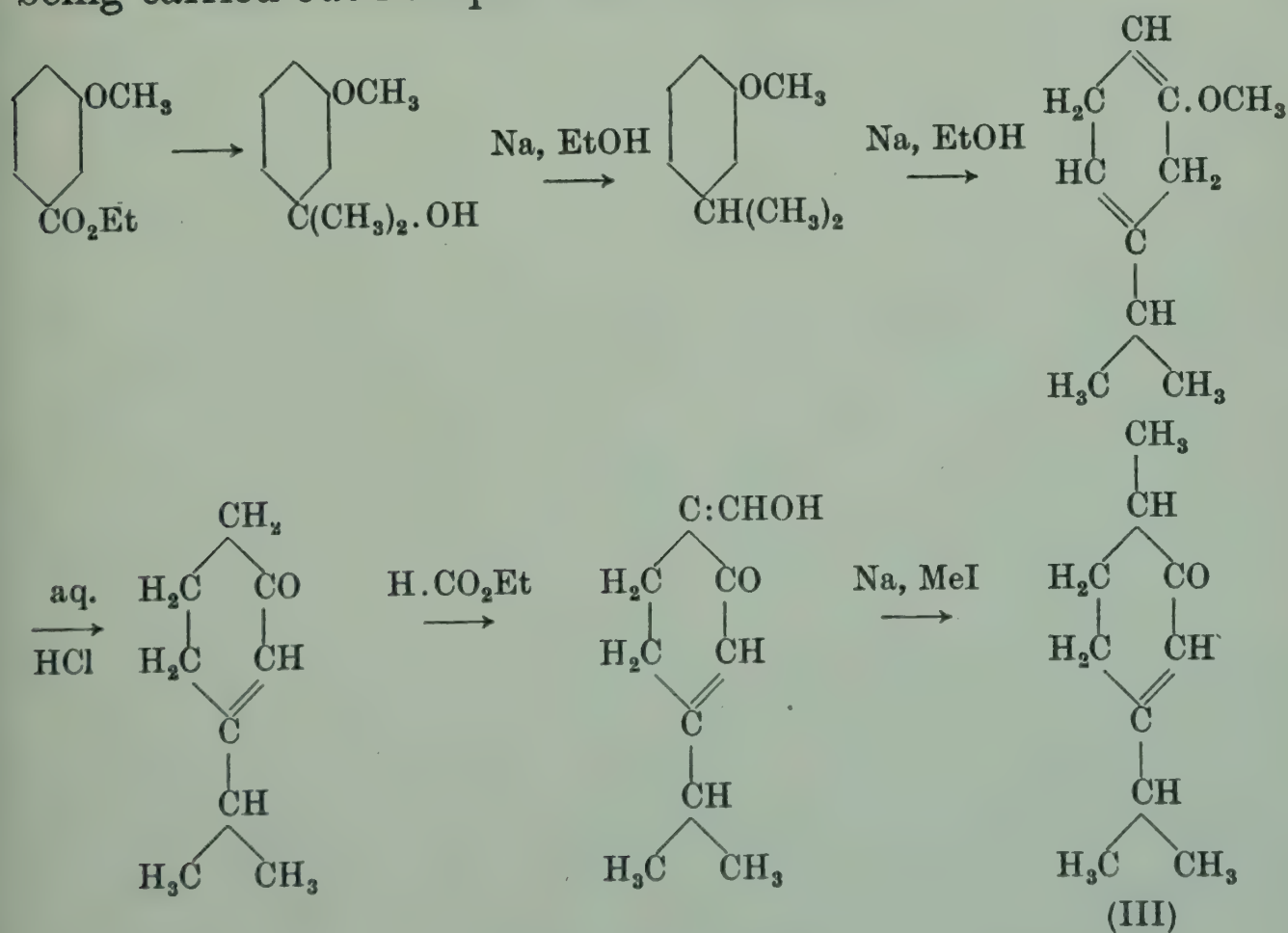
† *Annalen*, 1949, 561, 165.

‡ *Chem. Ber.* 1948, 81, 200, 206; 1949, 82, 112.

propenyl ketone gives (II). On treatment with hot dilute sulphuric acid, this undergoes "ketonic" hydrolysis and also cyclisation to yield *carvenone* (III), b.p. 97–99°/9.5 mm., n_D^{20} 1.4880 (*semicarbazone*, m.p. 200–202°).



Carvenone (2:4-dinitrophenylhydrazone, m.p. 165°) has also been synthesised by Birch and Mukherji* by reduction of carvacryl 2-hydroxyethyl ether with sodium in liquid ammonia, and also, by the series of reactions outlined below, from *ethyl m-methoxybenzoate* (IV), the reductions with sodium and alcohol being carried out in liquid ammonia solution.



* J.C.S. 1949, p. 2531.

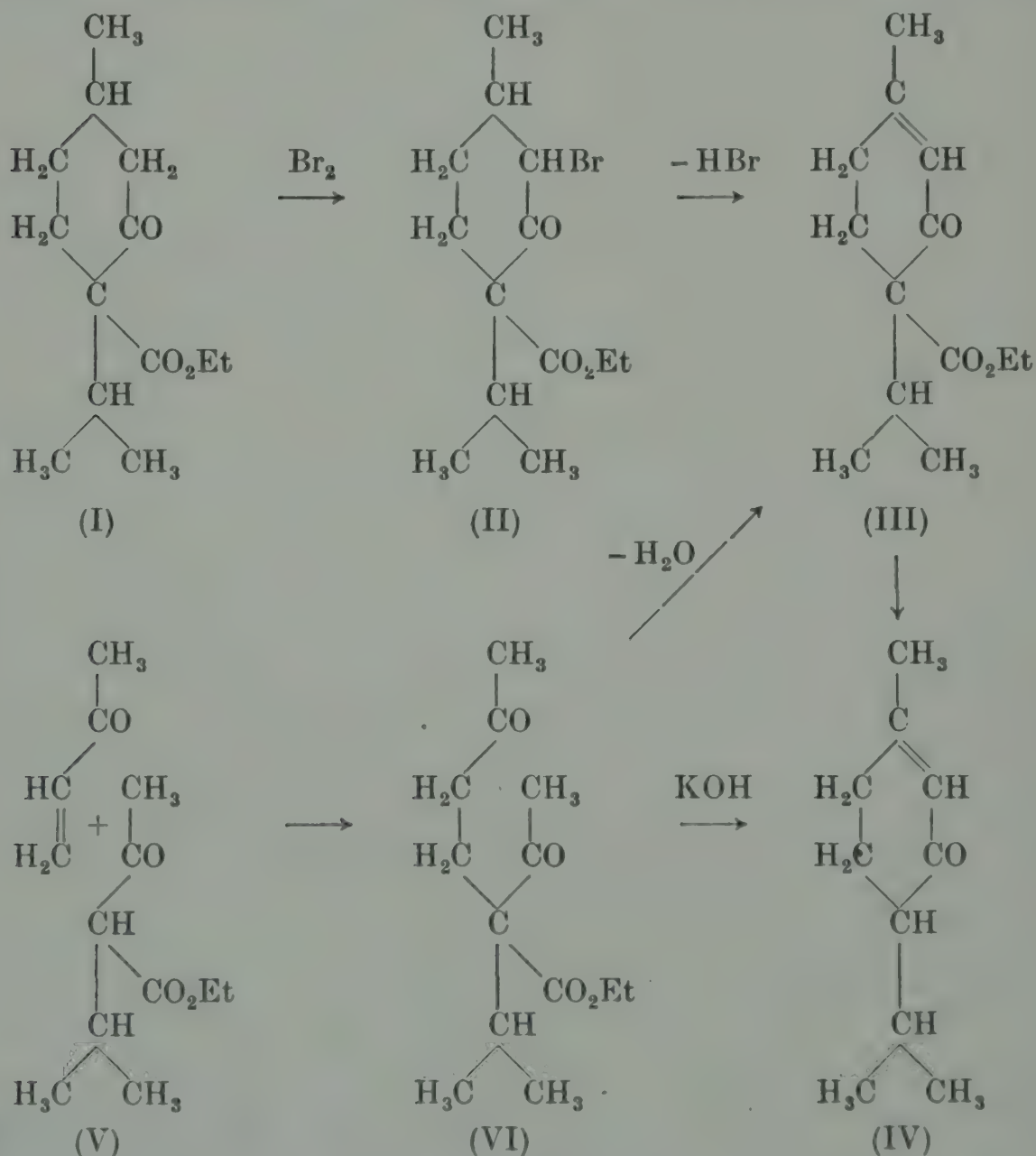
A general method for the synthesis of alicyclic ketones, including carvenone, has been propounded by Downes, Gill and Lions.*

PIPERITONE

(Vol. I, p. 359)

Several new synthesis of piperitone have recently been described. Chaudhuri[†] used a method very similar to that which led to a synthesis of menthone (compare Vol. I, p. 316); the synthetic *ethyl menthan-3-one-4-carboxylate* (I) on bromination gave (II), which on dehydrobromination to (III), followed by ketonic hydrolysis, gave piperitone (IV).

Henecka,[‡] by condensation of methyl vinyl ketone with *ethyl*



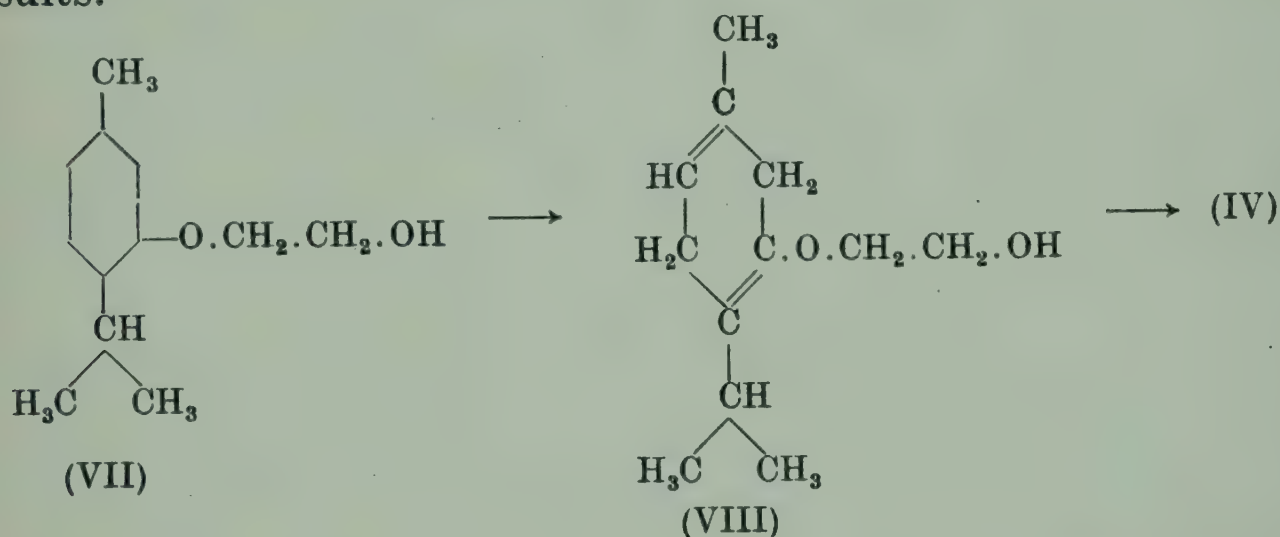
* *Austral. J. Sci.* 1948, 10, 147.

† *Science and Culture*, 1948, 13, 348.

‡ *Chem. Ber.* 1948, 81, 200, 206; 1949, 82, 112.

isopropylacetoacetate (V), obtained the *diketo-ester* (VI). Aldol-type cyclisation of this diketone can theoretically occur in two ways, to give either an *o*- or a *p*-menthene derivative, but by treatment with dry hydrogen chloride, followed by heating with diethylaniline it was possible to obtain *ethyl p-menth-1-ene-3-one-4-carboxylate* (III) as the main product. Ketonic hydrolysis with 95 per cent sulphuric acid then gave *dl*-piperitone (IV), b.p. $101^{\circ}/9.5$ mm., n_D^{20} 1.4870. Alternatively, it was found that treatment of (VI) with alcoholic potassium hydroxide gave piperitone directly.

Birch and Mukherji,* by reduction with sodium in liquid ammonia of *thymyl 2-hydroxyethyl ether* (VII), followed by acid hydrolysis of the resulting dihydro-derivative (VIII), have obtained piperitone. The glyceryl ether of thymol gives similar results.



A general scheme for the synthesis of alicyclic ketones, including piperitone, has been described by Downs, Gill and Lions.[†] Reference has already been made (p. 524) to the conversion of menthone into piperitone.

PULEGONE

(Vol. I, p. 370)

Treatment of pulegone with mercuric acetate gives 2-acetoxypulegone, b.p. $151-153^{\circ}/16$ mm., d_4^{20} 1.043, n_D^{20} 1.4855.[‡]

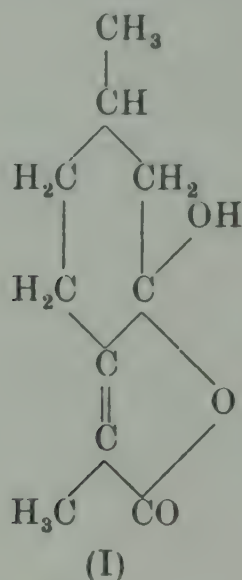
The oxide, *menthofuran* (Vol. I, p. 385), has been shown to occur in peppermint oil from *Mentha piperita vulgaris* S.; it gives

* J.C.S. 1949, p. 2531.

[†] Austral. J. Sci. 1948, 10, 147.

[‡] Treibs and Bast, *Annalen*, 1949, 561, 165.

an intense blue-violet colour with bromine in carbon tetrachloride.* When menthofuran undergoes autoxidation it gives the *lactone* (I), m.p. 188° , $[\alpha]_D -61.6^{\circ}$ (in alcohol), the structure of which has been proved by Woodward and Eastman.† This is



probably identical with the substances of similar melting-point obtained by the autoxidation of pulegone‡ and isolated from oil of pennyroyal.§

CARVONE

(Vol. I, p. 394)

According to Bachstetz and Cavallini^{||} dl-carvone hydrate (*hydroxy-carvotanacetone*), b.p. $232-234^{\circ}$, d^{24}_{D} 0.920, n_D 1.4800 (*semi-carbazone*, m.p. 174°), is present in the oil from *Boswellia Bhandagana*, and is identical with that obtained by Knoevenagel from carvone (see Vol. I, p. 403). Specimens prepared from carvone, however, are crystalline (m.p. $41-42^{\circ}$) and optically active.

* Bedoukian, *J. Amer. C.S.* 1948, **70**, 621.

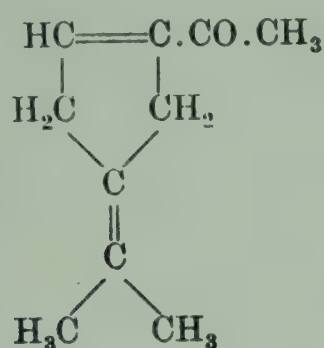
† *J. Amer. C.S.* 1950, **72**, 399.

‡ Sernagiotto, *Gazzetta*, 1917, 47, **1**, 150.

§ Naves, *Perfum. essent. Oil Rec.* 1945, p. 121.

|| *Farmaco sci. e. tec.* 1946, **1**, 254.

1-ACETYL-4-ISOPROPYLIDENECYCLO-
PENTENE



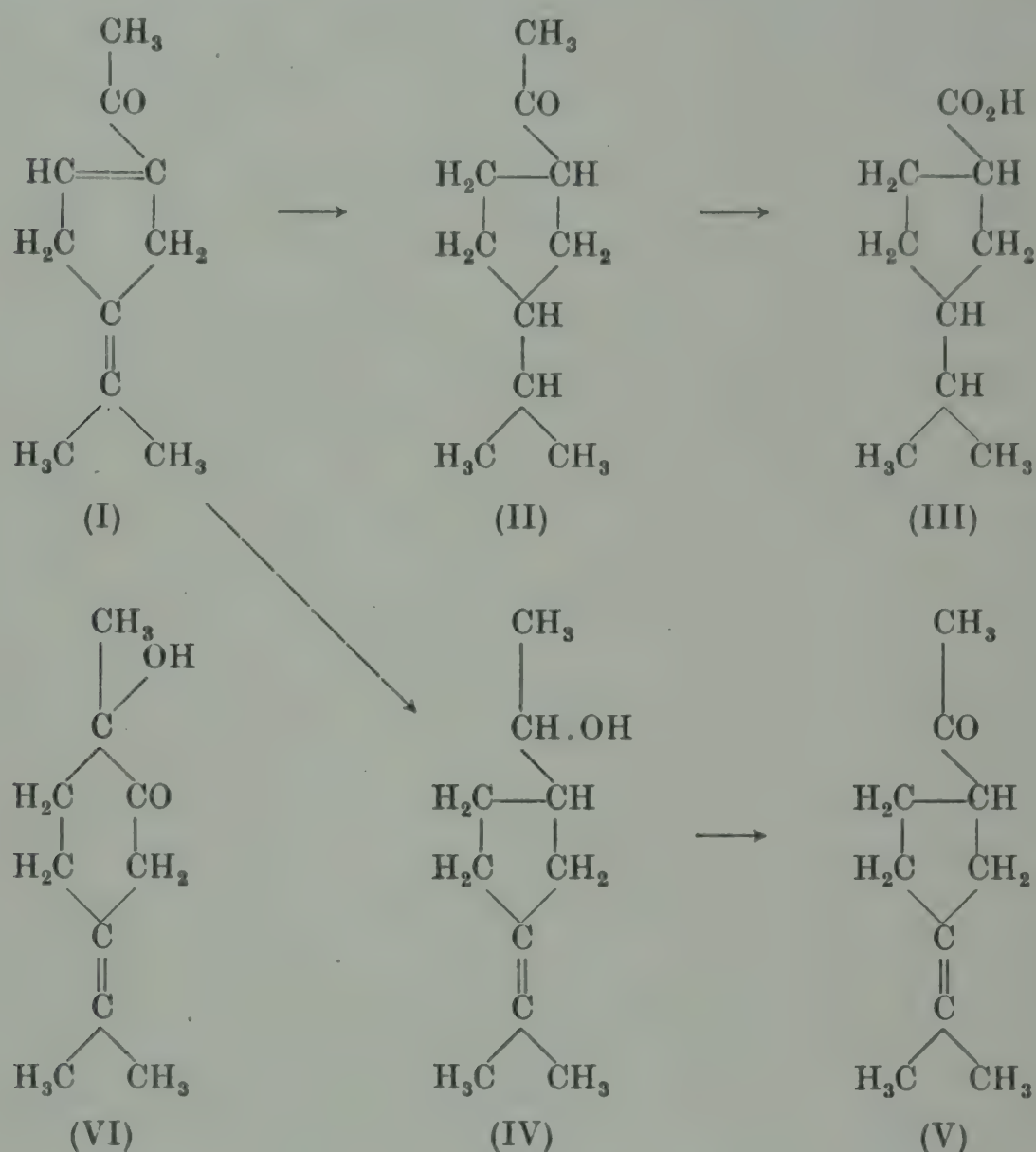
A new ketone, $\text{C}_{10}\text{H}_{14}\text{O}$, from *Eucalyptus Globulus*, described as having a kummel- and anise-like odour, has been isolated by Schmidt,* who recorded f.p. 5.2° , b.p. 225° , $d^{15^\circ} 0.9534$, $n_D^{20^\circ} 1.4947$, $\alpha_D \pm 0$. The molecular refraction (obs. 46.24) suggested a monocyclic, doubly unsaturated compound, with single conjugation. It had ketonic properties, and gave a *semicarbazone*, m.p. 202° , and an *oxime*, m.p. $66-67^\circ$; on hydrogenation over nickel it yielded 1-acetyl-3-isopropylcyclopentane (II)[†] which on oxidation with sodium hypobromite gave 3-isopropylcyclopentanecarboxylic acid (III). Conjugation of one double bond with the keto-group was suggested not only by the molecular refractivity, but by the formation of an *oxide*, $d^{15^\circ} 1.043$, $n_D^{20^\circ} 1.4783$ (*semicarbazone*, m.p. 181°), by treatment with alkaline hydrogen peroxide. Excess hydroxylamine on the ketone gave only a normal oxime, which indicated that the second double bond was not in conjugation and was therefore exocyclic;[‡] this was confirmed by reduction of the ketone with sodium in moist ether, when *pinolol* (IV), $d^{15^\circ} 0.926$, $n_D^{20^\circ} 1.4777$, $\alpha_D \pm 0^\circ$, was obtained, giving *pinolone* (V) (Vol. I, p. 441) on oxidation. The most probable structure for the ketone is therefore 1-acetyl-4-isopropylidenecyclopentene (I). The isopropylidene, rather than the isopropenyl, side chain is preferred because of the optical inactivity of the ketone; unfortunately, no ozonolysis was reported.

The ketone contains two isoprene units arranged in the conventional head-to-tail form, but is unusual in the terpene field

* *Chem. Ber.* 1947, **80**, 528, 533. † Wallach, *Annalen*, 1912, **392**, 69.

‡ When the semicarbazone is hydrolysed with sulphuric acid, this exocyclic double bond moves into the ring, to give an isomer (*semicarbazone*, m.p. 215°) of the original ketone, which was not obtained pure.

in being a simple *cyclopentene* derivative. It is possible that it does not actually exist as such in nature, and may perhaps be formed by pinacolic change from a precursor, such as $\Delta^{4(8)}$ -*p*-menthen-1-ol-2-one (VI).



ASCARIDOLE

(Vol. I, p. 446)

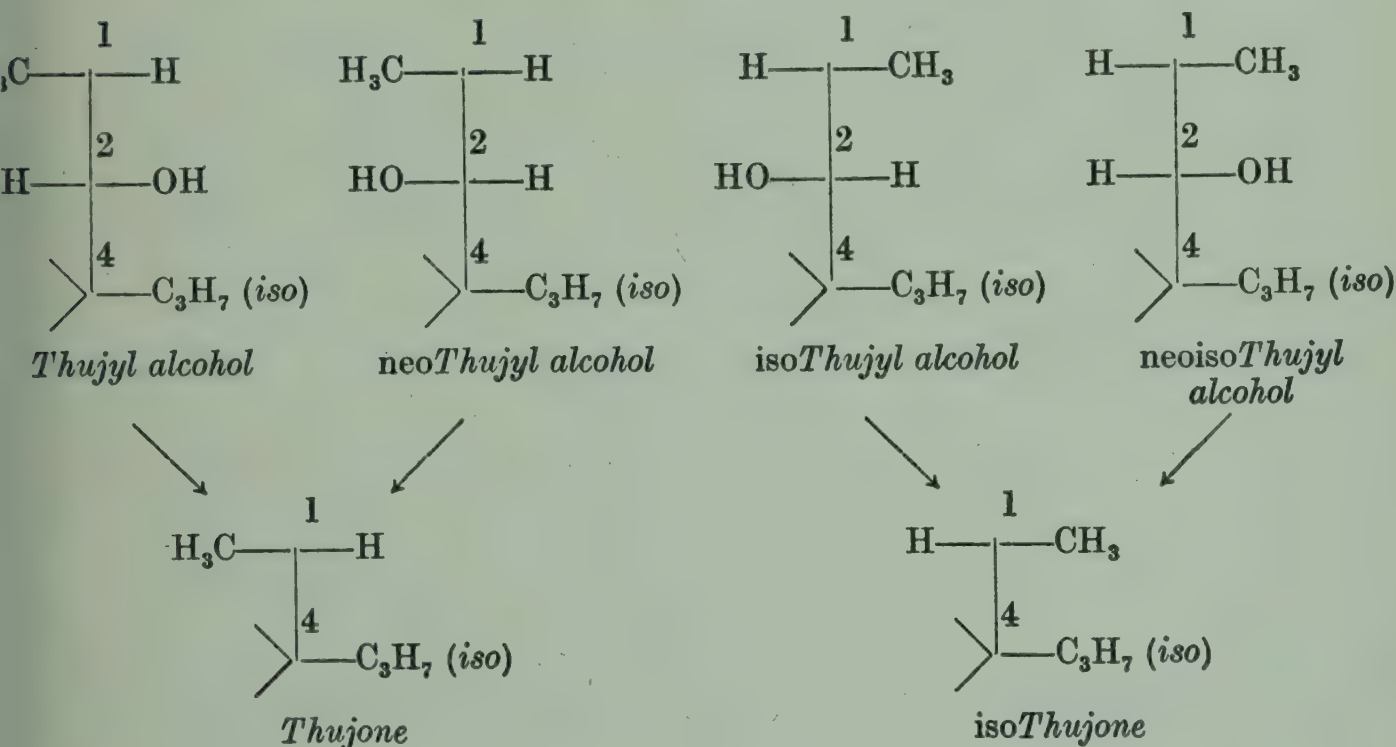
Szmant and Halpern* have reported the following constants for a highly purified sample: f.p. 5° , b.p. $75^{\circ}/1.5$ mm., $d_{25}^{25^{\circ}}$ 1.0061, $n_D^{25^{\circ}}$ 1.4718. Ultra-violet and infra-red spectra are also recorded.

* *J. Amer. C.S.* 1949, 71, 1133.

THUJYL ALCOHOL

(Vol. II, p. 23)

Barton* and Cram† have independently concluded that the Tschugaev reaction, in which dehydration of an alcohol is accomplished by pyrolysis of the methyl xanthate, proceeds by *cis*-elimination, and can consequently be used in certain cases to determine the configuration of the alcohol. Barton has pointed out that *l*-neothujyl alcohol in this way gives β -thujene, whilst *d*-isothujyl alcohol gives α -thujene (see Vol. II, p. 27); it follows, therefore, that in *isothujyl* alcohol the hydroxyl at C₂ is *cis*- with respect to the hydrogen at C₁, the reverse being so with *neo*-thujyl alcohol. The complete configurational relationships can be expressed as follows (compare Vol. II, p. 26):



EUCARVONE

(Vol. II, p. 85)

The direct formation of β -dihydroeucarvone (Vol. II, p. 91) from eucarvone, by hydrogenation in alcohol at ordinary temperature and pressure, over Raney nickel, has been reported by Naves and Ardizio.‡

* J.C.S. 1949, p. 2174.

† J. Amer. C.S. 1949, 71, 3883.

‡ *Helv. Chim. Acta*, 1949, 32, 329.

α-PINENE

(Vol. II, p. 105)

The kinetics of the hydrogenation of α - and β -pinenes have been studied by Smith, Fuzek and Meriwether.*

Thiolacetic acid reacts with α -pinene to give a product $C_{12}H_{20}OS$, b.p. 132–135°/13 mm.; $[\alpha]_D + 17.9^\circ$ from *l*-, and -26.6° from *d*-pinene.†

More recent investigations‡ on the action of *N*-bromosuccinimide on α -pinene have indicated that a complex mixture is formed (compare Vol. II, p. 169).

PINOCAMPHEOL

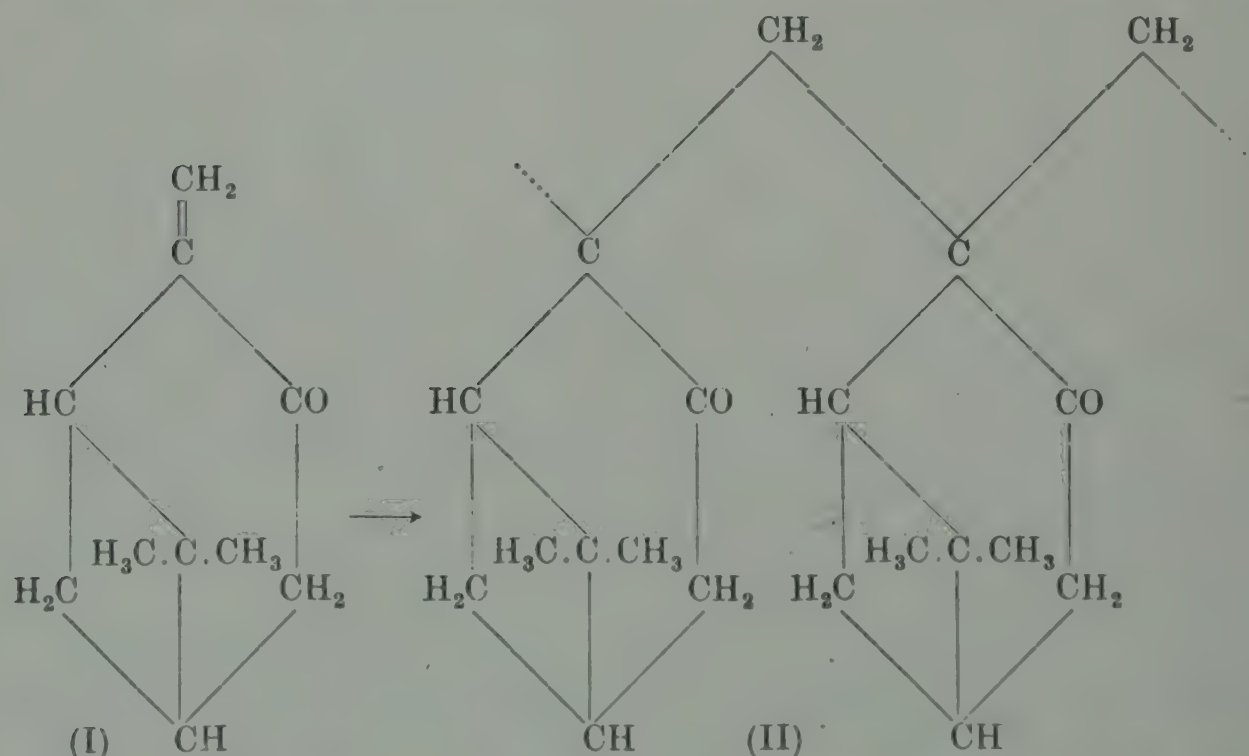
(Vol. II, p. 205)

Formulae (Ia) and (Ib), on p. 208, should be interchanged.

PINOCARVONE

(Vol. II, p. 240)

The well-known instability of pinocarvone (I) has been investigated by Treibs and Schmidt.§ Polymerisation is rapid on

* *J. Amer. C.S.* 1949, 71, 3765.† Behringer, *Annalen*, 1949, 564, 233.‡ Dupont, Dulou and Defay, *Bull. Soc. chim.* 1949, p. 310; Roberts and Trumbull, *J. Amer. C.S.* 1949, 71, 1630.§ *Chem. Ber.* 1949, 82, 218.

heating, particularly in the presence of air, and the polymer is formulated as (II), since it gives no formaldehyde on ozonisation, whilst on oxidation with permanganate it gives norpinic acid.

SANTENONE

(Vol. II, p. 257)

Mukherji* has described a new synthesis of homosantenic acid.

CAMPHENE

(Vol. II, p. 280)

Swann and Cripwell† have shown that camphene and tricyclene form an equilibrium mixture, in the presence of hydrated magnesium sulphate, or titanium dioxide, at the boiling-point.

The reaction between camphene and thiolacetic acid gives an oil, $C_{12}H_{20}OS$, b.p. $147-148^{\circ}/14$ mm.‡

With *N*-bromosuccinimide, camphene gives a mixture, but the main product is ω -bromocamphene.§

CAMPHENILONE

(Vol. II, p. 367)

Noyce|| has shown that when camphenilone is treated with concentrated sulphuric acid it gives *p*-methylacetophenone. The mechanism of this rearrangement, for details of which the original paper should be consulted, involve transformations both of the Nametkin and Wagner-Meerwein types; the investigation also throws light on the rearrangement of fenchone to 3:4-dimethylacetophenone (Vol. II, p. 573).¶

* *Science and Culture*, 1948, **13**, 258.

† *Ind. Chemist*, 1948, **24**, 573.

‡ Behringer, *Annalen*, 1949, **564**, 233.

§ Roberts and Trumbull, *J. Amer. C.S.* 1949, **71**, 1630.

|| *J. Amer. C.S.* 1950, **72**, 924.

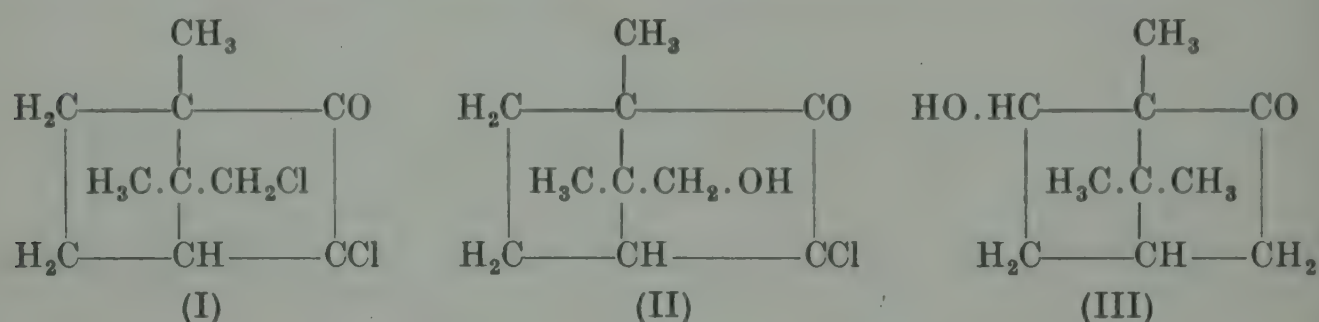
¶ For a recent review on molecular rearrangements in the terpene field, see Owen, *Perf. Essent. Oil Rec.* 1950, **41**, 4.

CAMPBOR

(Vol. II, p. 373)

The reduction of camphor by the Ponndorf method, using various alkoxides, has been investigated by Jackman, Macbeth and Mills;* the main product is *isoborneol*.

According to Ishidate,[†] when α -dihalogeno-camphors are heated with the alkali salts of fatty acids the π -position reacts preferentially; saponification then gives the α -halogeno- π -hydroxy-camphor. $\alpha\pi$ -Dichloro-camphor (I), for example, can be converted into α -chloro- π -hydroxycamphor (II), m.p. 130°.



The formation of 3-hydroxycamphor by phytochemical reduction of camphorquinone has been reported by Neuberg and Peiser.[‡]

dl-6-Hydroxycamphor (6-ketoborneol) (III), m.p. 130° (*semi-carbazone*, m.p. 200°; 3:5-dinitrobenzoate, m.p. 146°), has been isolated in very small yield by reduction of 2:6-diketocamphane with zinc dust and hydriodic acid at -10° (compare Vol. II, p. 427). On oxidation with chromic acid it gives α -campholonic acid.[§]

CAMPHORIC ACID

(Vol. II, p. 478)

Toivonen and his co-workers have described an interesting total synthesis of camphoric acid.^{||} Nearly fifty years ago, Perkin, Thorpe and Walker[¶] condensed ethyl $\alpha\alpha'$ -dibromo- $\beta\beta$ -dimethyl-

* *J.C.S.* 1949, p. 2641.† *Japanese P.* 161965.‡ *Advances in Carbohydrate Chemistry*, Vol. IV, p. 89.§ Asahina and Tukamoto, *Ber.* 1937, **70**, 584.|| Toivonen, Niininen, Eskola, Lang, Turunen and Tuhkanen, *Acta Chem. Scand.* 1948, **2**, 597.¶ *J.C.S.* 1901, **79**, 729.

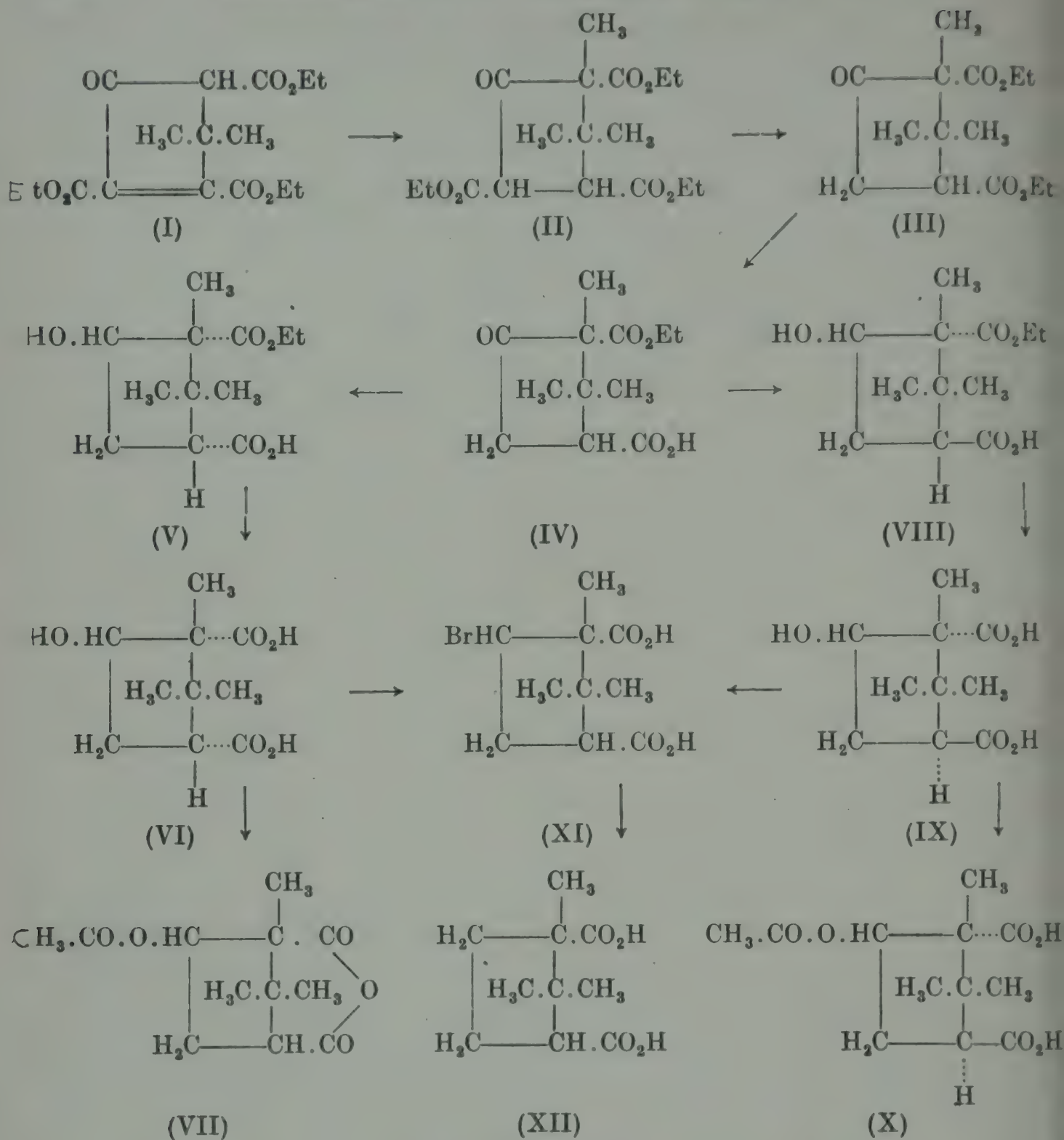
glutarate with ethyl sodiomalonate and obtained a product which they considered to be dicyclic, but which must now be formulated as the unsaturated compound (I). The methylated product, formed by reaction of the sodio-derivative with methyl iodide, on reduction gives (II). When this compound is hydrolysed with acid or with alkali, the tertiary carboxyl group is eliminated, but by treatment of (II) with hot aqueous glycerol the carbethoxy-group in the other β -position is preferentially eliminated to give diethyl 5-ketocamphorate (III). Unsuccessful attempts were made to reduce this by the Clemmensen and Kishner-Wolff methods to camphoric ester. Partial hydrolysis, in acid or alkaline solution, gave the β -ethyl mono-ester (IV) in two forms, *cis*-, m.p. 106° , and *trans*-, m.p. 150° (*semicarbazones*, m.p.s 228° and 226° respectively).

Electrolytic reduction of the *cis*-mono-ester gave the β -ethyl 5-hydroxy-*cis*-camphorate (V) as a mixture of two forms, differing in stereochemical structure at the 5-position, one of which was a solid, m.p. $111-112^{\circ}$, and the other a liquid; on hydrolysis these gave the two forms, m.p.s $207-208^{\circ}$ and 194° respectively, of 5-hydroxy-*cis*-camphoric acid (VI), which on treatment with acetyl chloride gave the 5-acetoxycamphoric anhydrides (VII), m.p.s $115-116^{\circ}$ and 124° . The formation of these anhydrides proved that the series of compounds belonged to the *cis*-camphoric acid group.

Electrolytic reduction of the *trans*-mono-ester (IV) gave ethyl 5-hydroxy-*trans*-camphorate (VIII), m.p. 116° , from which 5-hydroxy-*trans*-camphoric acid (IX), m.p. 240° , was obtained by hydrolysis; although two forms of these compounds are theoretically possible, only the one was actually found. Treatment of (IX) with acetyl chloride gave 5-acetoxy-*trans*-camphoric acid (X), m.p. 233° .

5-Hydroxycamphoric acid was converted into camphoric acid *via* the 5-bromo compound (XI) (obtained by reaction with hydrogen bromide in acetic acid), which was then reduced with zinc in acetic acid. Partial change of configuration occurred during the reaction, so that from either the *cis*- or *trans*-hydroxy-acid a mixture of *cis*- and *trans*-camphoric acid (XII) was obtained.

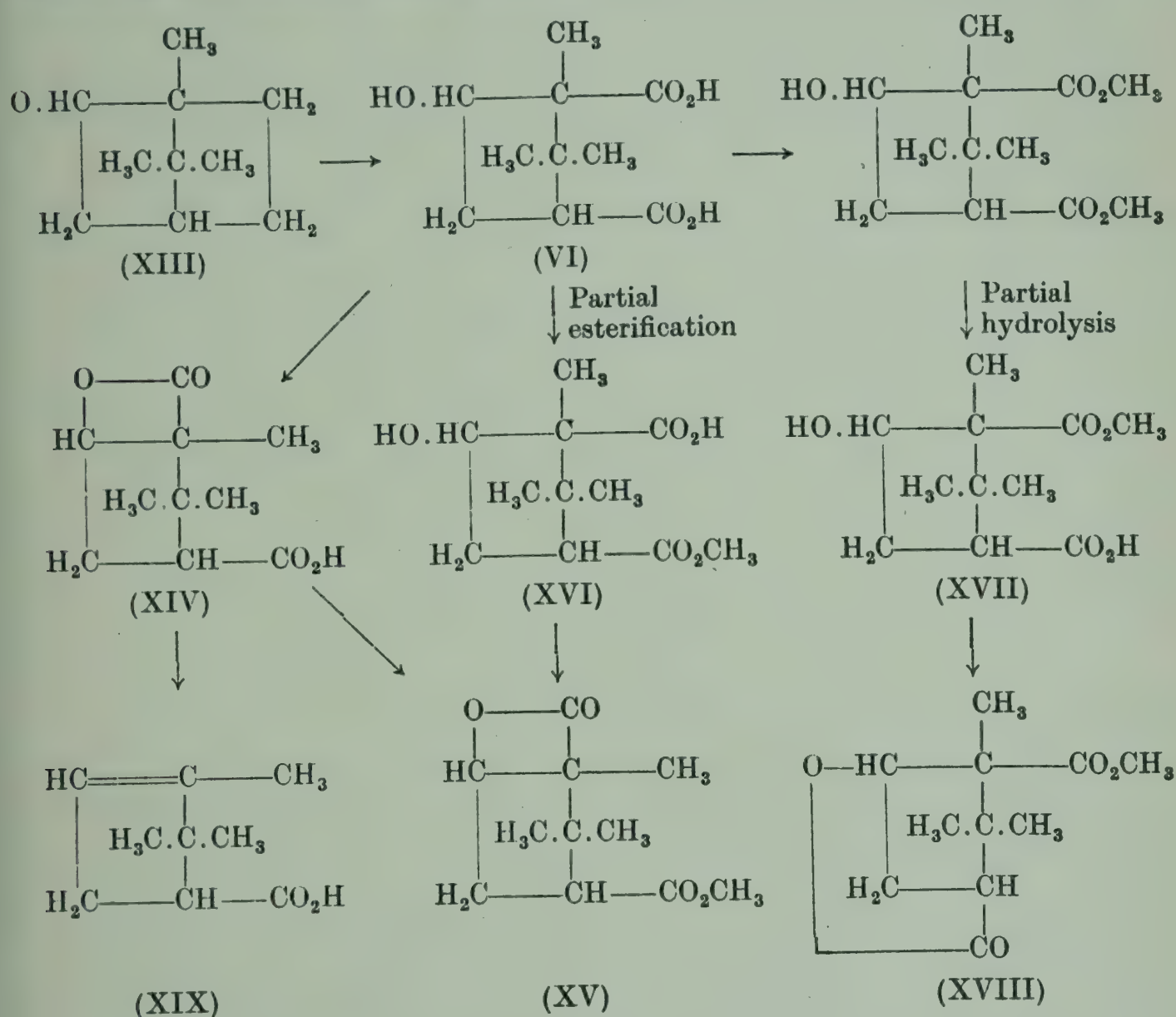
It has already been mentioned (Vol. II, p. 362) that 5-hydroxy-



camphoric acid can be obtained from borneol (XIII) or *iso*-borneol, but that only when derived from the former alcohol does it give a lactonic acid, thus supporting the *endo*-structure for borneol. Toivonen* has carried out further investigations on these reactions, and concludes that the lactonic acid is not, as previously supposed, of the γ -type, but is the β -lactonic acid (XIV); on treatment with diazomethane it gives the β -lactonic ester (XV), which is also formed by dehydration with acetyl chloride of the α -methyl ester (XVI) of 5-hydroxycamphoric

* Private communication.

acid (VI). The true γ -lactonic ester (XVIII) is obtained by the action of acetyl chloride on the β -methyl ester (XVII). When heated, the β -lactonic acid (XIV) gives α -campholytic acid (XIX). These observations do not affect the conclusions regarding the stereochemical structures of borneol and *isoborneol*.



Rothstein and Saville* conclude, from the study of reactions involving aluminium chloride, that the conversion of camphoric anhydride into *isolauronolic* acid (see Vol. II, p. 494) does not involve the intermediate formation of α -campholytolactone, but proceeds by way of a pinacolic displacement within the carbonium ion derived from the initial reaction of the anhydride with aluminium chloride.

* *J.C.S.* 1949, p. 1961.

FENCHYL ALCOHOL

(Vol. II, p. 552)

On some earlier theories of the mechanism of epimerisation of alcohols, which involved the existence of hydrogen in the α -position to the carbinol group, fenchyl alcohol, which does not possess such an α -hydrogen atom, would be expected to be resistant towards epimerisation by, for example, alcoholic alkoxides. Doering and Aschner, however,* have found that such theories are untenable, and that epimerisation of some alcohols containing α -hydrogen is completely inhibited by rigid exclusion of oxygen, peroxides, and carbonyl compounds; they conclude that epimerisation probably occurs by a Ponndorf-type reaction through the presence of traces of the corresponding ketones, and find that α - and β -fenchyl alcohols are readily interconverted in the presence of the very mobile fluorenol-fluorenone oxidation-reduction system.

FENCHONE

(Vol. II, p. 560)

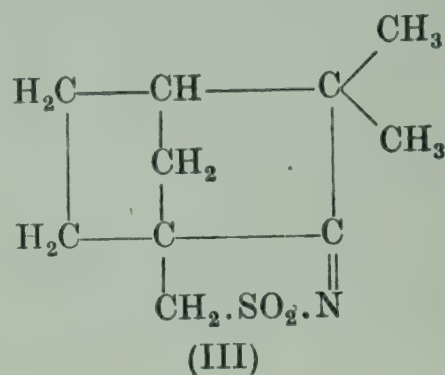
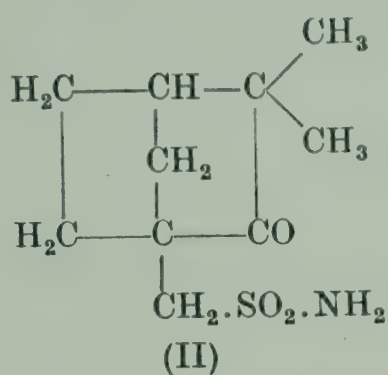
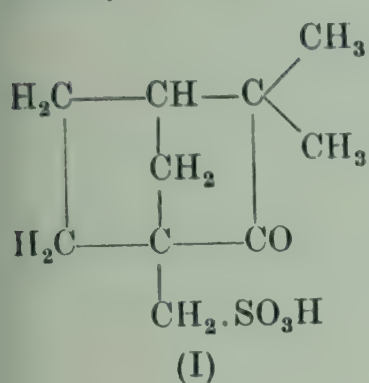
By treatment of *d*-fenchone with sulphur trioxide, Treibs and Lorenz† have obtained a *d-fenchonesulphonic acid* which crystallises with one molecule of water and has m.p. 68° , $[\alpha]_D^{23^\circ} + 26.3^\circ$ (in water), $+ 35.6^\circ$ (in chloroform). It gives a *methyl ester*, m.p. 49° , $[\alpha]_D^{22^\circ} + 40^\circ$ (in chloroform); an *acid chloride*, m.p. 52° , $[\alpha]_D^{25^\circ} + 23.6^\circ$ (in carbon tetrachloride); and an *anilide*, m.p. 96.5° , $[\alpha]_D^{19^\circ} + 46.3^\circ$ (in alcohol).

The *amide*, m.p. 103° , $[\alpha]_D^{18^\circ} + 46^\circ$ (in chloroform) on dehydration gives an *anhydramide*, m.p. 141.5° , $[\alpha]_D^{15^\circ} + 97.6^\circ$ (in chloroform), and this, together with other physical evidence, suggests that the compounds are ω -, rather than π -derivatives. The sulphonic acid, amide, and anhydramide are therefore provisionally given the structures (I), (II) and (III). (Compare the behaviour of camphor- ω -sulphonamide, Vol. II, p. 421.)

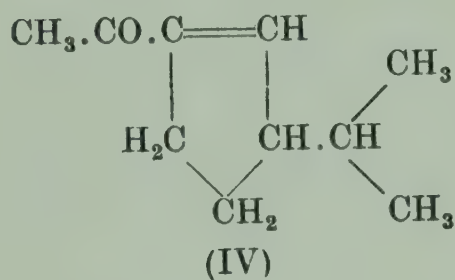
Reduction of the sulphonyl chloride with zinc and hydrochloric acid gives the corresponding *thiol*, as an oil, $d_4^{20^\circ} 1.070$,

* *J. Amer. C.S.* 1949, **71**, 838.† *Chem. Ber.* 1949, **82**, 400.

$[\alpha]_D^{14} + 19.5^\circ$ (in chloroform), which on oxidation with ferric chloride gives the *disulphide*, m.p. 63° , $[\alpha]_D^{12} - 51.4^\circ$ (in chloroform).



isoCamphor, obtained by the action of sulphuric acid on per-nitrosophenone and by other methods, is 1-acetyl-3-isopropyl- Δ^1 -cyclopentene (IV), and is not a *cyclohexenone* derivative (compare Vol. I, p. 441; Vol. II, pp. 441, 576).



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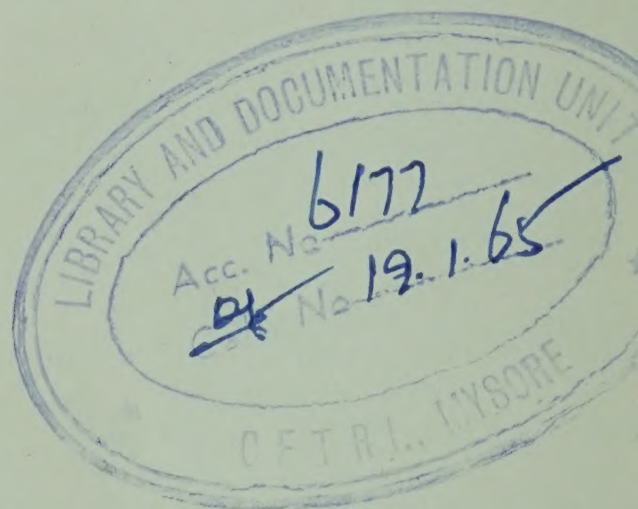
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